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Assessment of Serum Zinc Levels in Children with Attention-Deficit Hyperactivity Disorder

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ABSTRACT

Background & objective: Attention-deficit hyperactivity disorder (ADHD) is a highly prevalent neurodevelopmental condition linked to imbalances in neurotransmitter systems. Zinc (Zn), an essential cofactor in these metabolic pathways, has been implicated in ADHD pathogenesis. Given the high prevalence of Zn deficiency in the region and a critical gap in local data, this study aimed to assess and compare serum Zn levels in children with ADHD versus age-matched healthy children in Bangladesh.

Methods: This was a cross-sectional study conducted in Dhaka, enrolling a total of 60 children aged 4 to 12 years: 30 newly diagnosed children with ADHD (Case Group) and 30 apparently healthy controls (Control Group). Baseline characteristics of the two study groups encompassed age, body mass index (BMI), gender, maternal and obstetric history, family history of ADHD, maternal infection during pregnancy, low birth weight etc. Serum Zn levels were measured and were compared between the two study groups using the independent Sample t-Test.

Results: The two groups were statistically comparable in terms of age and body mass index (BMI). However, the ADHD group exhibited a male predominance ($p = 0.021$) and a significantly higher rate of positive family history for the disorder ($p = 0.011$). The mean serum Zn level was significantly lower in the ADHD group (86.06 ± 17.64 µg/dl) compared to the control group (95.20 ± 15.91 µg/dl) ($p = 0.032$). While the average serum Zn levels were lower in the ADHD group for both males (86.9 ± 17.4 µg/dl) and females (80.5 ± 21.1 µg/dl) compared to their control counterparts (94.0 ± 14.1 µg/dl and 97.8 ± 18.1 µg/dl, respectively), these differences were not statistically significant in the individual gender subgroups ($p = 0.159$ for males, $p = 0.133$ for females). The study found no notable difference in serum Zn levels between preschool-age children (86.03 ± 17.82 µg/dl) and school-age children (86.08 ± 18.05 µg/dl) within the ADHD group ($p = 0.995$).

Conclusion: Children with ADHD demonstrated significant deficiency in serum Zn compared to their healthy counterparts. However, this difference is not statistically significant when looking at males and females separately. Age (under or over 6 years) does not appear to affect zinc concentration within the ADHD group. These findings reinforce the biochemical link between Zn and ADHD and strongly suggest that routine micronutrient screening (particularly Zn) and targeted nutritional interventions may serve as beneficial ancillary strategies in the clinical management of children with ADHD.

Keywords: Attention Deficit Hyperactivity Disorder (ADHD), DSM-5, Zinc etc.

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INTRODUCTION:

Attention-deficit hyperactivity disorder (ADHD) is a highly prevalent neurodevelopmental disorder affecting approximately 5 to 8% of school-aged children globally.[1] It is characterized by persistent patterns of developmentally inappropriate inattention, hyperactivity, and impulsivity.[2] The symptoms often persist, with 60 to 80% of affected children meeting diagnostic criteria in adolescence and up to 60% continuing to exhibit symptoms into adulthood.[1] The disorder is classified by the DSM-5 into predominantly inattentive, predominantly hyperactive-impulsive, and combined presentations, with boys generally showing a higher prevalence.[3,4] The associated behavioral challenges adversely impact families, relationships, and school performance, resulting in substantial personal and social burden.[5]

The etiology of ADHD is multifactorial, involving a strong genetic component (60–80% heritability) and significant environmental influence (10 to 40% variance).[6,7] Pathophysiologically, ADHD involves abnormalities in frontal-subcortical pathways and an imbalance in dopaminergic and nor-adrenergic systems.[8] Given the rapid development of the brain during childhood, nutritional status plays a critical role, as malnourishment can impair processes like cell division and myelination.[5] Micronutrients are crucial for brain development and functioning, suggesting that deficiencies may increase the risk of ADHD.[3]

Among the essential micronutrients, zinc (Zn) is particularly relevant. Zinc deficiency is a recognized public health issue globally, particularly in developing nations in South Asia, including Bangladesh, where the prevalence of deficiency is inaapreciably high.[9,10] In the context of ADHD, inattention is a hallmark of Zn deficiency.[11] Zinc is an important cofactor for the metabolism of neurotransmitters, such as dopamine.[12] It also regulates neuronal excitability by mediating the release of glutamate and GABA.[13] Furthermore, Zn protects brain proteins from oxidative stress.[8] Consequently, Zn deficiency has been linked to abnormalities in mood, motor activity, cognition, and specifically to ADHD.[8] Previous studies have reported a decrease in serum Zn levels in children with ADHD, with an estimated deficiency prevalence of about 26%.[12,14]

Addressing ADHD symptoms through a nutritional approach is increasingly favored due to parental concerns regarding the side effects of long-term stimulant medication.[15] Despite the known global link between Zn status and ADHD, there is a scarcity of published data on the elemental status of children with ADHD in Bangladesh.[16] This study was designed to determine the serum zinc level in children newly diagnosed with ADHD compared to age-matched healthy controls. Early detection and correction of Zn deficiency may represent a valuable measure to reduce disease severity, symptoms, and potential future complications.

METHODS

This cross-sectional analytical study was conducted in Dhaka Medical College, Dhaka over a one-year period (January 2024 to December 2024). The study received ethical approval from the Ethical Review Committee, and concerned departmental authorities prior to commencement. The study was carried out across multiple clinical and academic sites, including the Department of Physiology, and the Department of Paediatrics, Dhaka Medical College, the Department of Paediatric Neurology, Bangladesh Shishu Hospital and Institute, Dhaka, and the Department of Biochemistry and Molecular Biology, Bangladesh Medical University (BMU), Dhaka.

A total of 60 children were enrolled in the study-30 children with ADHD as the Case Group and 30 age-matched apparently healthy children as the Control Group. In both study and control groups participating children were 4 to 12 years old, irrespective of genders. While children specific to Case Group were newly diagnosed cases of ADHD (according to DSM-5 criteria by a paediatric neurologist), children specific to Control Group were apparently healthy children, confirmed by parents to be in good physical and mental health. However, children were excluded if they had any other diagnosed neuropsychiatric disorders, including autism spectrum disorder, developmental delay, epilepsy, or mental retardation, or if they had any other chronic systemic illness. Participants were excluded from both groups if they had metallic implants (including dental amalgam fillings) or a history of supplementation (vitamins and minerals) in the last two months prior to enrollment. Serum samples were collected from both groups to assess Zn levels. Zinc measurement was done by direct colorimetric determination of zinc concentration in serum. This method relies on the use of specific coloring reagents, known as chromogens, which form a colored complex with zinc ions that can then be quantified spectrophotometrically. Zinc ions in the sample react with a chromogenic agent (dye) to produce a colored complex, 5-Br-PAPS (2-5-bromo-2-pyridilazo-5-N- propyl N-sulfo-propylamino phenol), a stable colour complex the intensity of which is directly proportional to the concentration of zinc ions and is measured at a specific wavelength using a spectrophotometer or a microplate reader.

Data were analyzed using SPSS (Statistical Package for Social Sciences) version 26.0. While quantitative variables (e.g., serum Zn levels, anthropometric data) were compared between the two study groups using an independent sample t-Test, qualitative variables were compared between groups using a Chi-square (χ^2) Test. Furthermore, biochemical variables were compared within specific age groups (pre-school and primary school) and gender categories (male and female) using an independent Student's t-Test. The level of significance was set at 5% and a p-value < 0.05 was considered a statistically significant difference.

RESULTS

Baseline Characteristics

The mean age of children in the Case Group was 6.90 ± 2.50 years, and that in the Control Group was 6.26 ± 1.90 years (p = 0.268), confirming that the groups were well age-matched. Similarly, the mean body mass index (BMI) did not differ significantly between Case (19.58 ± 1.24 kg/m^2) and Control Groups (19.78 ± 1.85 kg/m^2) (p = 0.628). However, a statistically significant difference was observed in the gender distribution between the two groups (86.7% vs. 13.3%, p = 0.021), reflecting the typical boy-to-girl ratio reported in ADHD populations (Table I).

Comparison of maternal and obstetric history revealed several notable differences between the groups (Table I). A family history of ADHD or similar symptoms was staggeringly higher in the Case Group (26.7%) compared to the Control Group (3.3%) (p = 0.011). Furthermore, a history of maternal infection during pregnancy (36.7% vs. 10%, p = 0.015) and low birth weight (30% vs. 3.3%, p = 0.006) were markedly higher in the ADHD group (Table I).

ADHD Subtype Distribution

Among the children in the ADHD group (n = 30), the subtypes, as categorized by the DSM-5, one-third (33.3%) presented with predominantly hyperactive-impulsive disorder, 10% with predominantly inattentive disorder, and 56.7% with combined characteristics (Fig.1).

Serum Zinc Levels

The overall mean serum zinc concentration was significantly lower in the ADHD group compared to the control group (86.06 ± 17.64 vs. 95.20 ± 15.91 µg/dl, p = 0.032). Subgroup analysis based on gender showed that while the mean serum Zn

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levels were lower in the ADHD Group than those in the Control Group in males (86.9 ± 17.4 vs. 94.0 ± 14.1 μg/dl, p = 0.159) they were fairly comparable in females (30.08 ± 3.47 vs. 28.7 ± 3.01 μg/dl, p = 0.133), these differences did not reach statistical significance within the respective gender subgroups likely due to the small sample size (n = 4 in ADHD female group) (Table II). However, subgroup analysis, based on age (< 6 and ≥ 6 years), revealed that serum Zn was fairly comparable between preschool- and school-aged children with ADHD (86.03 ± 17.82 vs. 86.08 ± 18.05, p = 0.995) (Table III).

Table I: Comparison of baseline characteristics between the study groups

Characteristic	Group		p-value
	Case (n=30)	Control (n=30)	
Age# (years)	6.90 ± 2.50	6.26 ± 1.90	0.268#
BMI (kg/m²)	19.58 ± 1.24	19.78 ± 1.85	0.628#
Gender (M/F)	26(86.7)/4(13.3)	18(60.0)/12(40.0)	0.021**
Family history of ADHD	8(26.7%)	1(3.3%)	0.011*
Maternal Age at delivery (years)	30.08 ± 3.47	28.7 ± 3.01	0.105#
Maternal Infection while pregnant	11(36.7%)	3(10.0%)	0.015**
Low Birth Weight History	9(30.0%)	1(3.3%)	0.006*

Categorical data were presented **n(%);** quantitative data were presented as **mean** ± **SD.** # Data were analyzed using **Unpaired t-Test** and were analyzed using Chi-squared (χ^2) Test; ***Fisher's Exact Test** was employed to analyze the data.

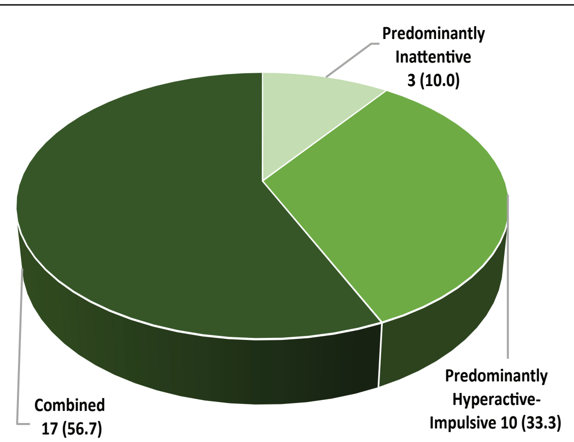

Figure 1: Pie chart showing distribution of the study subjects according to DSM- 5 symptoms scale in group A (n = 30)

Table II: Association between serum zinc level and sex in ADHD and Control Groups

Sex	Serum Zinc (μg/dl)		p-value
	Case (n=30)	Control (n=30)	
Overall (Male & Female)	86.06 ± 17.64	95.20 ± 15.91	0.032#
Male	(n = 26)	(n = 18)	
	86.9 ± 17.4	94.0 ± 14.1	0.159*
Female	(n = 4)	(n = 12)	
	30.08 ± 3.47	28.7 ± 3.01	0.133*

#Data were analyzed using **Unpaired t-test** and were presented as **mean** ± **SD;** **data were analyzed using Mann Whitney **Test and** was presented as **median** ± **SEM.**

Table III: Association between serum zinc level and sex in ADHD Group

Serum Zinc (μg/dl)	Age (years)		p-value
	< 6 (Pre-school Age) (n = 12)	≥ 6 (School Age) (n = 18)	
	86.03±17.82	86.08±18.05	0.995*

#Data were analyzed using **Mann Whitney Test** and were presented as **median** ± **SEM**.

DISCUSSION

Overview and Baseline Findings

Attention-deficit hyperactivity disorder (ADHD) is a chronic developmental disorder characterized by core deficits in attention and behavioral control, contributing significantly to impaired academic and adaptive functioning.[17] While pharmacological and behavioral interventions are standard, the documented side effects associated with long-term stimulant use prompt the search for alternative, non-pharmacological measures, particularly those related to nutritional status.[15] This study, conducted in Bangladesh, aimed to investigate the trace element, serum zinc (Zn) status in children with newly diagnosed ADHD compared to healthy controls.

The baseline analysis confirmed that the ADHD and control groups were well-matched in terms of age (p =0.268) and BMI (p=0.628), consistent with findings from other studies.[11,18] The significant male predominance observed in the ADHD group (Male:Female ratio of 6.5:1, p=0.021) is in agreement with global epidemiological data for ADHD and regional reports.[13,19]

Associated Clinical and Obstetric Factors

Several socio-demographic and clinical findings supported the complex, multifactorial etiology of ADHD. Notably, a positive family history of ADHD or similar disorders was significantly higher in ADHD than in the control group (26.7% vs. 3.3%, p = 0.011), reinforcing the strong genetic and familial component of the disorder.[14] Furthermore, adverse perinatal factors, including a history of low birth weight and maternal infection during pregnancy, were also significantly more frequent in the ADHD group. This is consistent with literature linking these environmental factors to increased ADHD risk.[20,21] Conversely, sociodemographic parameters like maternal age showed no significant difference, aligning with some regional data.[17]

The distribution of ADHD subtypes in this cohort showed a dominance of the Combined Presentation (56.7%), followed by the Hyperactive-Impulsive presentation (33.3%). The low rate of the Inattentive presentation (10%) may reflect clinical presentation bias, where hyperactivity is often the primary cause for seeking medical consultation and subsequent diagnosis during the early school years.[11]

Serum Zinc Status in ADHD

The central finding of this study was the significantly lower mean serum Zn level observed in children with ADHD (86.06 ± 17.64 μg/dl) compared to the healthy controls (95.20 ± 15.91 μg/dl) (p = 0.032). This finding is consistent with a large body of international research that has implicated Zn deficiency in the pathogenesis and severity of ADHD symptoms.[3,11,18] Zinc is a critical trace element essential for the synthesis and metabolism of major neurotransmitters, particularly dopamine, and plays a vital role in regulating neuronal excitability and protecting against oxidative stress in the brain.[8,13] Deficiency, which is already endemic in South Asian populations,[10] may act as a crucial environmental trigger or mediator in genetically susceptible children, contributing to the neurobiological impairments seen in ADHD.

Subgroup analysis based on gender showed that although serum Zn was lower in ADHD children of both sexes, the differences were not statistically significant in the male (p = 0.159) or female (p=0.133) subgroups. This lack of significance, particularly in the female subgroup, is most likely attributable to the small sample size of girls in the ADHD group (n = 4), limiting statistical power.

Limitations

The primary limitation of this study is its cross-sectional design, which prevents the establishment of a causal relationship between low serum Zn (and other micronutrients) and ADHD. Secondly, the small sample size of female participants limits the ability to draw robust, statistically significant conclusions regarding gender-specific mineral status. Future studies employing a larger, longitudinal design are recommended to confirm these findings and evaluate the therapeutic efficacy of Zn supplementation in this population.

CONCLUSION

This study concludes that children with ADHD in Bangladesh exhibit significantly lower mean serum zinc levels compared to age-matched healthy children, supporting the role of Zn deficiency as a potential biological marker or contributing factor to the disorder. However, this difference is not statistically significant when looking at males and females individually. Age does not act as a determinant of zinc concentration in children with ADHD.

The findings advocate for the inclusion of serum Zn assessments in the routine clinical evaluation of children diagnosed with ADHD, particularly in regions prone to endemic deficiency. Early detection and nutritional intervention may serve as an effective ancillary measure to reduce the severity of symptoms and prevent future complications.

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