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Assessment of Serum Ferritin and Magnesium Levels in Children with Attention-Deficit Hyperactivity Disorder

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ABSTRACT

Background & objective: Attention-deficit/hyperactivity disorder (ADHD) is a multifactorial neurodevelopmental disorder. While genetics play a major role, environmental factors such as mineral deficiencies (Iron and Magnesium) are increasingly implicated in its pathogenesis due to their roles in neurotransmitter synthesis and brain metabolism. This study was designed to measure and compare the levels of serum ferritin and magnesium in children with ADHD against an apparently healthy control group in Bangladesh.

Methods: This cross-sectional study was conducted in the Department of Physiology, Dhaka Medical College, from January 2024 to December 2024. A total of 60 children aged 4–12 years were enrolled: 30 newly diagnosed ADHD cases (per DSM-5 criteria) and 30 age-matched healthy controls. Data collection included demographic and clinical factors such as age, geneder, body mass index (BMI), family history of ADHD, maternal infection while pregnant, and birth weight etc. Serum ferritin was measured via sandwich chemiluminescence immunoassay, and serum magnesium (Mg) was measured using a photometric color test. Statistical analysis was performed using independent student's t-tests and chi-square tests via SPSS version 26.0.

Results: Statistical analysis showed that the groups were well-matched for age and body mass index. However, gender distribution and family history differed significantly; the ADHD cohort demonstrated a notably higher proportion of male participants ($p = 0.021$) and a more frequent family history of the condition ($p = 0.011$) compared to the control group. A Sgnificantly lower mean serum ferritin levels were observed in the ADHD group compared to the control group (31.44 ± 20.87 ng/ml vs. 45.14 ± 20.60 ng/ml; $p = 0.013$). Similarly, mean serum magnesium levels were significantly lower in children with ADHD (1.80 ± 0.26 mg/dl vs. 2.13 ± 0.31 mg/dl; $p < 0.001$). Within the ADHD group, pre-school children (aged < 6 years) exhibited significantly lower Mg levels than primary school-aged children (1.71 ± 0.22 mg/dl vs. 1.90 ± 0.22 mg/dl; $p = 0.011$). Ferritin and Mg levels were also significantly lower in male ADHD subjects compared to male controls.

Conclusion: Children with ADHD exhibit significantly lower levels of serum ferritin and magnesium compared to healthy children. These findings suggest that micronutrient deficiencies are common comorbidities in ADHD, particularly in younger children and males, highlighting the potential for nutritional screening and intervention in clinical management.

Keywords: Attention Deficit Hyperactivity Disorder (ADHD), DSM-5, serum ferritin, magnesium etc.

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INTRODUCTION:

Attention-deficit hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder that transcends childhood, often persisting into adolescence and adulthood. Characterized by developmentally inappropriate levels of inattention, impulsivity, and hyperactivity, it affects approximately 5% to 8% of school-aged children globally.[1] According to the World Health Organization, it is among the most frequent neurobehavioral disorders, significantly interfering with daily functioning, academic achievement, and social relationships.[2]

The etiology of ADHD is multifactorial, involving a complex interplay between genetics and environment. While hereditary factors account for a substantial portion of cases, environmental variables specifically nutritional status mediate a significant percentage of ADHD variance.[3] Micronutrients such as iron and magnesium are essential for the structural and functional integrity of the developing brain.

Iron serves as a critical cofactor for tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of dopamine.[4] A deficiency in iron, even before the onset of clinical anemia, can reduce dopamine receptor density and transport, leading to the frontal-subcortical pathway abnormalities often observed in ADHD patients.[5] Serum ferritin is considered the most reliable measure of these body iron stores.[6] Simultaneously, magnesium (Mg) plays a vital role in regulating neuronal excitability by acting as a physiological antagonist to the N-methyl-D-aspartate (NMDA) glutamate receptors.[7] Low Mg levels are associated with increased internalizing symptoms, such as anxiety and irritability, as well as externalizing behaviors like hyperactivity.[8]

In Bangladesh, the prevalence of micronutrient deficiencies is high; however, there is a scarcity of data regarding the elemental status of children specifically diagnosed with ADHD. This study was designed to bridge that gap by assessing serum ferritin and magnesium levels in a Bangladeshi pediatric cohort to determine if these nutritional markers differ significantly from healthy peers.

METHODS:

This cross-sectional analytical study was conducted over a one-year period, from January to December 2024, at Dhaka Medical College (DMC), Dhaka. Prior to commencement, the protocol received formal approval from the Ethical Review Committee (ERC) and relevant departmental authorities. The research was a collaborative effort involving the Departments of Physiology and Paediatrics at DMC, the Department of Paediatric Neurology at Bangladesh Shishu Hospital and Institute, and the Department of Biochemistry and Molecular Biology at Bangladesh Medical University (BMU).

The study subjects comprised 60 children, aged 4 to 12 years, divided into two distinct groups:

- Case Group (n=30): Consisted of newly diagnosed ADHD patients, as categorized by a paediatric neurologist according to DSM-5 criteria.
- Control Group (n=30): Formed of age-matched, apparently healthy children with no reported physical or mental health concerns.

To maintain study integrity, strict exclusion criteria were applied to both groups. Children were excluded if they presented with:

- Co-morbid neuropsychiatric disorders (e.g., autism spectrum disorder, developmental delay, epilepsy, or intellectual disability).
- Chronic systemic illnesses.
- Metallic implants (including dental amalgam) or a history of vitamin/mineral supplementation within the two months preceding enrollment.

Venous blood samples were collected to evaluate micronutrient (ferritin and magnesium) status. Laboratory assessments were centralized at the Department of Biochemistry and Molecular Biology, BMU, and included:

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- **Serum Ferritin:** Quantified using a sandwich chemiluminescence immunoassay.
- **Serum Magnesium (Mg):** Measured via a photometric colorimetric test. Serum ferritin was measured via sandwich chemiluminescence immunoassay, and serum magnesium was measured using a photometric color test at the Department of Biochemistry and Molecular Biology, BMU, Dhaka.

Data processing was performed using SPSS version 26.0. The following statistical measures were employed: While independent Sample t-Tests were used to compare quantitative variables (e.g., ferritin and magnesium levels) between the two groups, as well as for subgroup analyses based on gender and age (pre-school vs. primary school), Chi-square (χ^2) Tests were employed for the comparison of qualitative data. Statistical significance was established at a threshold of $p < 0.05$ (5% significance level).

RESULTS:

The study groups were statistically comparable regarding age and body mass index (BMI). The mean age was 6.9 ± 2.5 years for the Case Group and 6.3 ± 1.9 years for the Control Group (p=0.268). Similarly, no significant difference was observed in mean BMI between the Case (19.58 ± 1.24 kg/m^2) and Control groups (19.78 ± 1.85 kg/m^2, p = 0.628). However, gender distribution differed significantly, with the ADHD group showing a marked male predominance (86.7% vs. 13.3%, p = 0.021). Analysis of maternal and obstetric history also revealed significant disparities; the Case Group exhibited a higher prevalence of a positive family history of ADHD (26.7% vs. 3.3%, p = 0.011), maternal infection during pregnancy (36.7% vs. 10%, p = 0.015), and low birth weight (30% vs. 3.3%, p = 0.006), as detailed in Table I.

Within the Case Group (n = 30), the distribution of ADHD subtypes (according to DSM-5 criteria) showed that combined subtype of ADHD (hyperactive-impulsive and inattentive) was predominant (56.7%) followed by predominantly hyperactive-impulsive (33.3%) & predominantly inattentive (10.0%) (Fig.1).

The study found a significant reduction in both serum ferritin and magnesium (Mg) levels in the ADHD group (p = 0.013 and p = 0.001 respectively). Sub-group analysis showed that male children with ADHD had significantly lower ferritin (p = 0.019) and Mg (p = 0.003) compared to control males. Although serum ferritin levels of female children of case group was staggeringly lower than their control female counterparts, the difference did not reach the level of significance (18.2 ± 19.3 vs. 39.0 ± 18.3 ng/ml, p = 0.071). However, serum Mg of female cohort of case group did differ significantly with their control peers (1.9 ± 0.1 vs. 2.1 ± 0.3 mg/dl, p = 0.129) (Table II). Sub-group analysis revealed that serum Mg was significantly lower in preschool children (< 6 years) than the school-aged children (p = 0.011). Serum ferritin, though, much lower in the former cohort than the latter cohort, the difference did not reach the level of significance (p= 0.201) (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/m^2)	19.58 ± 1.24	19.78 ± 1.85	0.628#
Sex			
Male	26(86.7)	18(60.0)	0.021**
Female	4(13.3)	12(40.0)	
Family history of ADHD	8(26.7)	1(3.3)	0.011*
Maternal Age at delivery (years)	30.08 ± 3.47	28.70 ± 3.01	0.105#
Maternal infection while pregnant	11(36.7)	3(10.0)	0.015**
History of LBW	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;** **data were analyzed using Chi-squared (χ^2); ***Fisher's Exact Test** was employed to analyze the data.

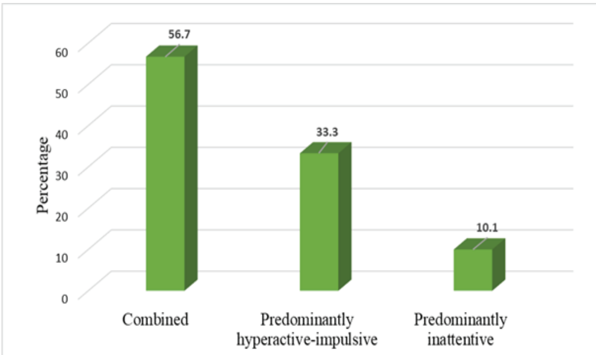

Figure 1: Showing distribution of the study subjects accordingto DSM- 5 symptoms scale in group A (n = 30)

Table II: Association of serum ferritin and nagnesium levels with ADHD

Variables	Group		p-value
	Case (n = 30)	Control (n = 30)	
Serum ferritin (ng/ml)	31.4 ± 20.8	45.1 ± 20.6	0.013#
Serum magnesium (mg/dl)	1.8 ± 0.3	2.1 ± 0.3	0.001#
Sub-group Analysis	Male (n = 26)	Male (n = 18)	
Serum ferritin (ng/ml)	33.5 ± 20.7	49.2 ± 21.6	0.019#
Serum magnesium (mg/dl)	1.8 ± 0.3	2.1 ± 0.3	0.003#
Sub-group Analysis	Female (n = 4)	Female (n =12)	
Serum ferritin (ng/ml)	18.2 ± 19.3	39.0 ± 18.3	0.071*
Serum magnesium (mg/dl)	1.9 ± 0.1	2.1 ± 0.3	0.129*

#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 Biomarkers	Age (years)		p-value
	< 6 (Pre-school Age) (n = 12)	≥ 6 (School Age) (n = 18)	
Serum ferritim (µg/dl)	25.4 ± 11.8	35.5 ± 24.7	0.201#
Serum magnesium (µg/dl)	1.7 ± 0.22	1.9 ± 0.22	0.011#

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

DISCUSSION:

The findings of this cross-sectional study demonstrate a significant reduction in serum ferritin and magnesium levels in children with ADHD compared to age-matched healthy controls. These results align with international literature suggesting that multiple micronutrient deficiencies often coexist in neurodevelopmental disorders like ADHD.[9,10]

Overview and Baseline Findings

Attention-Deficit Hyperactivity Disorder (ADHD) is a persistent neurodevelopmental condition defined by fundamental impairments in attention and impulse control, which frequently lead to significant challenges in academic performance and social adaptation.[11] Although standard treatment protocols typically involve behavioral therapy and medication, the potential for adverse effects from prolonged stimulant use has intensified interest in non-pharmacological alternatives, especially those concerning nutritional health.[12] This study, conducted in Bangladesh, sought to evaluate the status of serum micronutrients in children newly diagnosed with ADHD relative to a healthy control group.

The analysis of baseline data indicated that the ADHD and control cohorts were statistically equivalent in age (p = 0.268) and BMI (p=0.628), which aligns with established research in this field.[13,14] However, a notable male-to-female ratio of 6.5:1 (p = 0.021) was observed within the ADHD group. This distinct male predominance is consistent with both international epidemiological trends and regional clinical data.[15,16]

Associated Clinical and Obstetric Factors

The socio-demographic and clinical results of this study reinforce the multifaceted etiology of ADHD. A positive family history of the disorder was substantially more prevalent in the ADHD group than in the control group (26.7% vs. 3.3%, p=0.011), a finding that corroborates the significant hereditary and genetic influence on the condition.[17] Additionally, the ADHD group reported significantly higher rates of adverse perinatal events, such as maternal infection during pregnancy and low birth weight. These results are in agreement with existing literature that identifies these early environmental stressors as risk factors for ADHD development.[18,19] In

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contrast, variables such as maternal age did not show significant variance between groups, matching reports from other regional studies.[11]

The prevalence of ADHD subtypes in this study revealed that the combined presentation was most common (56.7%), followed by the hyperactive-impulsive subtype (33.3%). The relatively low frequency of the inattentive subtype (10%) might be attributed to a referral bias; hyperactive and impulsive behaviors are often more disruptive, prompting parents to seek medical consultation and diagnosis more readily during a child's early school years.[13]

The Role of Iron (Ferritin)

Our study observed significantly lower mean ferritin levels in the ADHD group (31.44 ± 20.87 ng/ml vs. 45.14 ± 20.60 ng/ml). This is clinically significant because iron is essential for the myelination of nerves and the catabolism of neurotransmitters. The reduction in ferritin likely impacts the dopaminergic and nor-adrenergic systems, which are the primary targets of conventional stimulant medications. Interestingly, male children with ADHD in our study showed a more pronounced deficiency compared to their control counterparts ($p = 0.019$), suggesting a possible gender-linked vulnerability to iron-deficiency-related cognitive symptoms.

The Role of Magnesium

The disparity in serum magnesium levels was even more striking ($p < 0.001$). Magnesium is crucial for the elimination of brain ammonia, which, if accumulated, can lead to impaired attention.[20] Our data revealed that pre-school children with ADHD had significantly lower Mg levels than primary-school-aged children within the same group ($p = 0.011$). This supports the hypothesis that magnesium deficiency may have its greatest impact during critical early developmental windows.[3] Lower Mg levels might lead to an over-activation of the NMDA pathway, manifesting as the "always on the go" behavior typical of the hyperactive-impulsive subtype.

Implications for Clinical Practice

The socio-demographic data in this study also highlighted that children with ADHD had a higher frequency of low birth weight and maternal infections, both of which are risk factors for early-life nutritional depletion. Given the side effects associated with long-term stimulant use, such as appetite suppression and sleep disturbances, addressing these underlying mineral deficiencies offers a promising adjunctive or preventative strategy.

By identifying these deficiencies early, clinicians in Bangladesh can implement targeted nutritional interventions such as iron or magnesium or both supplementation to potentially reduce the severity of ADHD symptoms and improve the overall adaptive functioning of these children.

Limitations

Every research project has constraints that influence the interpretation of its findings. The following limitations should be considered when evaluating the results of this study:

- **Study Design and Sample Size**

The use of a cross-sectional design allows for the identification of associations but precludes the establishment of a definitive causal relationship between micronutrient levels and ADHD. Furthermore, the relatively small sample size (n=60), particularly in female subgroup analyses, may limit generalization of the findings to broader pediatric population in Bangladesh.

- **Confounding Variables**

While the study matched for age and BMI, and excluded those on micronutrient supplements, other confounding factors such as dietary patterns, socioeconomic status, and physical activity levels were not exhaustively controlled.

- **Diagnostic Subjectivity and Referral Bias**

The diagnosis was based on DSM-5 clinical criteria, which, while the gold standard, relies on behavioral observations and parental reports. The lower prevalence of the "Inattentive" subtype in this study suggests a possible referral bias, as hyperactive behaviors are more likely to disrupt a household and prompt a clinical visit than inattentiveness.

- **Single Biochemical Measurement**

Serum levels of ferritin and magnesium were measured at a single point in time. These levels can fluctuate based on recent dietary intake or acute physiological stress. Furthermore, serum magnesium only represents a small fraction of the body's total magnesium stores (as most is stored in bones and soft tissues), and intracellular magnesium levels might have provided a more comprehensive view of the child's nutritional status.

To validate these results, subsequent research should utilize longitudinal frameworks and larger cohorts. Such studies are essential to determine the clinical benefits and therapeutic potential of magnesium and iron interventions for children with ADHD.

Conclusion

This study demonstrates that children with ADHD exhibit significantly lower levels of serum ferritin and magnesium compared to their healthy peers, suggesting a potential link between these micronutrient deficiencies & the pathophysiology of the disorder. The ADHD cohort was also characterized by a high prevalence of the combined subtype, a notable male predominance, and a strong association with hereditary and obstetric risk factors, such as family history of ADHD, maternal infection during pregnancy, and low birth weight.

Subgroup analysis highlights that while magnesium deficiency is more pronounced in pre-school aged children, the correlation between low iron stores (ferritin) and ADHD is particularly significant among males. These findings underscore the importance of screening for nutritional deficiencies in the clinical evaluation of ADHD. Addressing these biochemical imbalances through targeted nutritional interventions or supplementation may play a supportive role in the multi-modal management of the disorder, potentially improving behavioral outcomes in affected children.

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