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Biochemical Study of Norepinephrine and Selected Trace Elements in Children with Autism and Attention Deficit Hyperactivity Disorder in Thi-Qar Governorate, Iraq

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ABSTRACT

Background & Objective: Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are prevalent neurodevelopmental conditions characterized by cognitive, behavioral, and social impairments. Both disorders may involve disturbances in catecholamine regulation and trace element homeostasis. This study evaluated serum norepinephrine levels and selected trace elements (zinc, iron, magnesium, and copper) in children with ASD or ADHD compared with healthy controls in Thi-Qar Governorate, Iraq.

Materials & Methods: A case-control study was conducted between January 2024 and February 2025 and included 170 children aged 3 to 13 years: 55 with ASD, 60 with ADHD, and 55 healthy controls. Blood samples were obtained at the Autism Center in Thi-Qar Governorate and Shatra General Hospital under specialist supervision, following standard collection protocols. Serum norepinephrine and mineral concentrations were analyzed using validated biochemical methods.

Results: Children with ASD and ADHD demonstrated significantly elevated norepinephrine levels compared with controls (P <0.05). Concentrations of zinc, iron, and magnesium were significantly reduced (P <0.05), whereas copper levels were markedly increased in both clinical groups relative to healthy participants.

Conclusion: The findings indicate notable neurochemical and mineral alterations in children with ASD and ADHD. These results underscore the potential diagnostic value of norepinephrine and trace elements as biochemical markers and suggest the need for targeted nutritional and therapeutic interventions.

Keywords: Autism Spectrum Disorder (ASD), Norepinephrine, Trace Elements, Zinc, Magnesium, Copper, Attention-deficit/hyperactivity Disorder

1. Introduction

Autism spectrum disorder encompasses a diverse group of neurodevelopmental conditions marked by impairments in social interaction, communication difficulties, and repetitive behavioral patterns, as outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (1). Individuals with ASD typically exhibit deficits in social reciprocity, challenges in both verbal and nonverbal communication, along with stereotyped or ritualistic behaviors (2, 3).

Attention-deficit/hyperactivity disorder stands as one of the most common neurodevelopmental conditions worldwide, affecting approximately 5% to 7% of children and 2% to 5% of adults (4). The clinical presentation of ADHD is characterized by inattention, hyperactivity, and impulsivity, which manifests in three distinct subtypes: predominantly inattentive, predominantly hyperactive/impulsive, or combined presentation. This disorder significantly compromises functional abilities and developmental progress across various life domains (5).

Epidemiological data reveal substantial overlap between ADHD and other neurodevelopmental disorders. The concurrent occurrence with ASD is particularly significant, with comorbidity rates estimated between 30% and 50%. Such high comorbidity suggests common neurobiological substrates and poses considerable diagnostic and treatment challenges for healthcare providers (6).

Norepinephrine serves dual roles as a neurotransmitter and neuromodulator, contributing significantly to the pathophysiology of both ASD and ADHD. This endogenous catecholamine influences several cognitive processes, including attention, arousal, executive functioning, and stress reactivity (domains that are commonly impaired in these neurodevelopmental conditions). Aberrant noradrenergic signaling has been identified in individuals with ASD and may underlie deficits in social communication and stereotyped behavioral patterns (6, 7). In ADHD, noradrenergic dysfunction is associated with attentional deficits and executive impairments, forming the basis for pharmacological treatments that target norepinephrine reuptake inhibition, such as atomoxetine (8). Recent evidence indicates that genetic variations affecting norepinephrine transporter function and receptor expression may constitute shared risk factors for both disorders (9).

The role of trace elements (micronutrients essential in small amounts for normal physiological function) has received growing interest in ASD and ADHD research (10). Zinc acts as a cofactor in numerous enzymatic processes and is crucial for brain development, synaptic plasticity, and neurotransmission, while also serving as an antioxidant defense against oxidative damage. Several studies have identified zinc deficiency in children with ASD and ADHD when compared with typically developing peers (11). Insufficient zinc levels may impair neurodevelopmental processes and contribute to symptom manifestation by disrupting dopaminergic and noradrenergic neurotransmission pathways that regulate attention and behavior (12).

Iron is fundamental for oxygen delivery, mitochondrial energy production, brain development, and neurotransmitter synthesis. Serum ferritin, the main iron storage protein, functions as a biomarker of systemic iron reserves, with its concentrations indicating total body iron availability. Iron deficiency has been linked to cognitive dysfunction and behavioral abnormalities characteristic of both ASD and ADHD (13). Multiple studies have shown reduced serum ferritin levels in affected children, while iron supplementation interventions have demonstrated improvements in attention span and reductions in hyperactive behaviors (14, 15).

Magnesium serves as a cofactor in hundreds of enzymatic processes and plays vital roles in synaptic communication and neuroplasticity. Research consistently shows lower magnesium concentrations in children with ASD and ADHD compared with control groups, and supplementation studies have revealed positive effects on hyperactivity and attentional performance (16). Magnesium regulates glutamatergic neurotransmission and affects dopaminergic and noradrenergic pathways, potentially explaining its importance in these neurodevelopmental disorders (17).

Copper functions as an essential cofactor for enzymes participating in neurotransmitter synthesis and metabolism; however, excess copper accumulation poses neurotoxic risks. Individuals with ASD and ADHD often display disrupted copper homeostasis, with numerous studies reporting elevated copper to zinc ratios (18, 19). These imbalances may compromise neurotransmitter function and elevate oxidative stress mechanisms that are implicated in the pathogenesis of both conditions (20).

The present investigation constitutes the first comprehensive assessment of serum norepinephrine levels and essential trace element profiles (zinc, iron, magnesium, and copper) in children diagnosed with ASD and ADHD in Thi-Qar Governorate, Iraq. This research fills an important gap in regional biomarker studies and offers new perspectives on the biochemical features of these neurodevelopmental disorders in a population characterized by unique environmental exposures, dietary habits, and genetic background. The results provide foundational reference data and may guide future therapeutic strategies specifically designed for this population.

2. Materials and Methods

2.1 Study Design and Setting

This case-control clinical study was conducted in 2024 in Thi-Qar Governorate, Iraq, across multiple clinical sites, including the Autism Center, the Autism Department at Shatra General Hospital, and selected private clinics under the supervision of specialist pediatricians. The study included 170 children aged 3–13 years, divided into three groups: 55 with Autism Spectrum Disorder (ASD), 60 with Attention Deficit Hyperactivity Disorder (ADHD), and 55 age- and sex-matched healthy controls.

2.2 Participant Selection

Participants were clinically assessed and diagnosed by qualified physicians in accordance with the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5). The diagnosis of autism spectrum disorder (ASD) was established based on persistent deficits in social communication and social interaction across various contexts, accompanied by restricted and repetitive behaviors, interests, or activities (21). The diagnosis of attention-deficit/hyperactivity disorder (ADHD) was determined by the presence of a sustained pattern of inattention and/or hyperactivity–impulsivity that interferes with daily functioning or development, with symptom onset before 12 years of age and impairment evident in multiple settings (22). Children with comorbid intellectual disabilities or diagnosed anemia were excluded from the study. Informed consent was obtained from all parents or legal guardians prior to participation.

2.3 Sample Size Determination

Sample size was determined through statistical power analysis using G*Power version 3.1.9.7 based on one-way ANOVA with α=0.05, power of 80%, and medium effect size (f=0.25) (23). The analysis indicated a requirement of 159 participants (53 per group) (24). To account for

potential attrition, the sample was increased to 170 participants: 55 with autism spectrum disorder, 60 with attention-deficit/hyperactivity disorder, and 55 neurotypical controls, ensuring adequate statistical power while maintaining clinical feasibility.

2.4 Sample Collection

Approximately 5 mL of venous blood was obtained from each participant under aseptic conditions by standard venipuncture. Samples were allowed to clot at room temperature in disposable centrifuge tubes and then centrifuged at 3000 × g for 10 minutes. The separated serum was stored at –20°C until further biochemical analysis.

2.5 Biochemical Assays

Serum norepinephrine concentrations were quantified using a commercially available Human Norepinephrine enzyme-linked immunosorbent assay (ELISA) kit (Catalog # ab287804, Abcam, Cambridge, United Kingdom) in accordance with the manufacturer's protocol. The assay demonstrated a minimum detection sensitivity of 0.1 ng/mL, with intra-assay and inter-assay coefficients of variation of <8% and <12%, respectively, confirming acceptable precision and reproducibility.

Serum trace element concentrations—including zinc (Zn), iron (Fe), magnesium (Mg), and copper (Cu)—were quantified via colorimetric spectrophotometry utilizing commercial analytical kits (Biolabo SA, Maizy, France) with measurements performed on a UV-Visible spectrophotometer (Model UV-1800, Shimadzu Corporation, Kyoto, Japan). All biochemical analyses were conducted in duplicate in accordance with the manufacturers' standardized protocols, with appropriate quality control materials included in each analytical batch to ensure measurement accuracy and reliability.

All statistical analyses were performed using SPSS software, version 20.0 (IBM Corp, Armonk, NY). Quantitative data are expressed as mean ± standard deviation (SD). Intergroup comparisons were evaluated using one-way analysis of variance (ANOVA) followed by the least significant difference (LSD) post hoc test to determine pairwise differences. Statistical significance was defined as a *P*-value less than 0.05.

3. Result

The study included a total of 170 participants divided into three groups: ASD (n = 55), ADHD (n = 60), and healthy controls (n = 55). Sex distribution was balanced across groups, with no statistically significant differences observed in male-to-female ratios ($p > 0.05$), indicating homogeneity in demographic characteristics as shown in Table 1.

3.1 Serum Norepinephrine Concentration

As shown in Table 2, children with ASD had significantly higher mean serum norepinephrine levels (4.91 ± 1.47 ng/mL) compared to those with ADHD (3.98 ± 0.54 ng/mL) and healthy controls (1.19 ± 0.26 ng/mL). The differences among all groups were statistically significant ($p \leq 0.05$).

3.2 Serum Zinc Concentration

The results revealed a significant reduction in serum zinc levels in children with Autism Spectrum Disorder (93.94 ± 17.37 µg/dL) and ADHD (97.81 ± 13.74 µg/dL) groups compared to the control group (103.05 ± 13.26 µg/dL). The difference between the patient groups was not statistically significant.

3.3 Serum Iron Concentration

The results show a significant decrease in serum iron levels in both the Autism Spectrum Disorder group (112.00 ± 13.95 µg/dL) and ADHD (115.24 ± 18.28 µg/dL) groups compared to the control group (126.00 ± 35.02 µg/dL). No significant difference was found between the two disorder groups.

3.4 Serum Magnesium Concentration

The results showed a significant decrease in serum magnesium levels in patients with Autism Spectrum Disorder (2.05 ± 0.35 mg/dL) and ADHD (2.14 ± 0.44 mg/dL) groups when compared with controls (2.46 ± 0.80 mg/dL). The patient groups did not differ significantly from each other.

3.5 Serum Copper Concentration

The results show a significant decrease in serum iron levels in both the Autism Spectrum Disorder group (126.80 ± 23.56 µg/dL) and ADHD (117.25 ± 18.65 µg/dL) groups compared to controls (104.67 ± 15.15 µg/dL). Copper levels were also significantly higher in ASD than in ADHD ($p \leq 0.05$).

Table 1. Demographic distribution of study participants by group and sex.

Groups	NO.	Gender (Male/Female)
Controls	55	28/27
ADHD	60	36/24
Autism	55	33/22

Table 2. Serum norepinephrine concentration of controls and patients groups.

Groups	No.	Norepinephrine (ng/mL) Mean ± SD
Controls	55	1.19±0.26 c
ADHD	60	3.98±0.54 b
Autism	55	4.91± 1.47 a
LSD		0.76

a: Each value represents mean ± SD with non-identical superscripts (a, b, c, etc.), indicating significant differences (p ≤ 0.05). N denotes the number of subjects. SD denotes standard deviation. ADHD: Attention Deficit Hyperactivity Disorder.

Table 3. Serum trace elements concentration of controls and patients groups.

Groups	NO.	Zinc (µg/dL) Mean ± SD	Iron (µg/dL) Mean ± SD	Magnesium (mg/dL) Mean ± SD
Controls	55	103.05 ± 13.26 ^a^	126.00 ± 35.02 ^a^	2.46 ± 0.80 ^a^
ADHD	60	97.81 ± 13.74 ^b^	115.24 ± 18.28 ^b^	2.14 ± 0.44 ^b^
Autism	55	93.94 ± 17.37 ^b^	112.00 ± 13.95 ^b^	2.05 ± 0.35 ^b^
LSD		6.00	9.74	0.23

a: Each value represents mean ± SD. Non-identical superscripts (a, b, c) within a column indicate significant differences (p ≤ 0.05). LSD: Least Significant Difference.

4. Discussions

This case–control study identified significant biochemical alterations in Iraqi children with autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). The findings demonstrated markedly elevated norepinephrine concentrations, reduced levels of zinc, iron, and magnesium, and concomitant copper accumulation compared with neurotypical controls.

The present study demonstrated significantly elevated serum norepinephrine concentrations in pediatric patients with autism and ADHD, corroborating earlier investigations that documented hyperactivity within the noradrenergic system in these neurodevelopmental conditions (25). Physiological evidence supporting this finding includes research demonstrating enlarged baseline pupillary diameter in autistic children, serving as a biomarker for heightened noradrenergic activity (26). Additional investigations have validated increased norepinephrine concentrations in both plasma and urinary specimens obtained from individuals with ASD (27). Within the ADHD population, scientific evidence indicates that excessive norepinephrine activity compromises prefrontal cortical function (28), with contemporary data revealing that elevated norepinephrine levels disrupt the neural capacity to filter task-irrelevant stimuli (29).

The pathophysiological mechanisms underlying norepinephrine elevation demonstrate disorder-specific characteristics. In autism, dysregulation of the locus coeruleus-norepinephrine system originates from impaired function of low-sensitivity α2 adrenergic receptors (30). This receptor dysfunction compromises the negative feedback mechanisms governing norepinephrine release, culminating in excessive neurotransmitter synthesis and cortical hyperexcitability. These alterations manifest clinically as attentional deficits, exaggerated stress reactivity, and perturbations in neural network equilibrium. Conversely, in ADHD, norepinephrine hyperactivity predominantly affects the prefrontal cortex, where it disturbs the balance of cortical arousal through its action on α2A adrenergic receptors localized to cortical layers II and III (31). This dysregulation impairs attentional control mechanisms and heightens impulsive behaviors. Genetic susceptibility factors, particularly mutations within the ADRA2A gene, modify receptor sensitivity and contribute to noradrenergic dysregulation (32).

Our analysis revealed significantly reduced zinc concentrations in both autism and ADHD cohorts relative to healthy controls, consistent with the substantial body of literature establishing zinc deficiency as a characteristic feature of neurodevelopmental disorders. Multiple investigations have documented marked zinc deficiency in autistic children (33), with systematic reviews confirming decreased zinc levels across the majority of studies examining autistic populations (34). Meta-analytic evidence provides robust support for reduced zinc concentrations in individuals diagnosed with ADHD (35).

At the molecular level, zinc deficiency disrupts synaptic architecture in autism through alterations in the SH3

domain of the SHANK3 protein, a critical scaffolding molecule at excitatory synapses (36). This disruption compromises Homer-Shank protein interactions, resulting in diminished postsynaptic receptor density and impaired synaptic transmission. These structural abnormalities may provide a mechanistic explanation for the communication and social deficits characteristic of autism by directly affecting long-term potentiation, the cellular substrate underlying learning and memory processes. In ADHD, zinc deficiency impairs the activity of zinc-dependent enzymes, notably delta-6-desaturase, which plays an essential role in fatty acid metabolism (37). Additionally, zinc deficiency affects dopaminergic regulation via D2 dopamine receptors, disrupting neural signaling within the cortical-striatal-thalamic circuits that are critical for attentional processes and motor control (38).

The current investigation documented decreased iron concentrations in both patient populations compared with controls, aligning with previous research establishing iron dysregulation in neurodevelopmental disorders. Studies have demonstrated reduced iron and ferritin concentrations in autistic children (39), while research in ADHD populations has established correlations between lower ferritin levels and symptom severity (40).

In autism, iron deficiency compromises myelination processes by reducing phospholipid synthesis necessary for myelin sheath formation (41). Furthermore, iron deficiency decreases neuronal energy production through impaired function of the mitochondrial electron transport chain, affecting neural signaling efficiency, particularly in long-range connectivity pathways essential for integrated brain function. In ADHD, iron deficiency results in dysfunction of tyrosine hydroxylase, the rate-limiting enzyme in dopamine biosynthesis, by reducing the availability of iron as an essential cofactor (42). This impairment decreases dopamine synthesis in the striatum and prefrontal cortex, brain regions critical for attention and executive function. Quantitative magnetic resonance imaging studies have confirmed significant iron reductions in the basal ganglia and substantia nigra of ADHD patients (43).

Our findings revealed decreased magnesium concentrations in both autism and ADHD groups, consistent with previous investigations documenting magnesium dysregulation in neurodevelopmental disorders. Studies have recorded reduced plasma magnesium in autistic children, and meta-analyses have confirmed decreased serum magnesium in ADHD populations (44). Research has established that magnesium deficiency exacerbates hyperactivity and inattention symptoms, demonstrating a functional relationship between magnesium status and clinical manifestations (45).

In autism, magnesium deficiency results in NMDA receptor hyperactivity through loss of voltage-gated calcium channel inhibition, causing neural hyperexcitability and disrupting the excitatory-inhibitory balance necessary for normal neural processing (46). This mechanism may explain the sensory hypersensitivity and processing abnormalities commonly observed in autism. In ADHD, magnesium deficiency impairs neurotransmitter regulation through effects on adenylate cyclase and cyclic AMP production while promoting neuroinflammation via NF-κB pathway activation. Given that magnesium maintains neural membrane stability through regulation of sodium-potassium pumps and neurotransmitter release mechanisms, deficiency states have widespread consequences for neural function (47).

Our study documented elevated copper concentrations in both autism and ADHD cohorts, with more pronounced elevations observed in autistic individuals. Previous investigations have demonstrated elevated copper levels and disrupted copper-to-zinc ratios in both autism and ADHD populations (48), suggesting that copper dysregulation may represent a common feature across neurodevelopmental disorders.

In autism, elevated copper induces oxidative stress through enhanced free radical production via Fenton-type reactions (49), while simultaneously inhibiting antioxidant defense systems, particularly superoxide dismutase. This dual mechanism causes neuronal injury and mitochondrial dysfunction, contributing to the metabolic abnormalities observed in autism. In ADHD, elevated copper disrupts the copper-to-zinc ratio, affecting metalloenzyme function, particularly dopamine-β-hydroxylase, which catalyzes the conversion of dopamine to norepinephrine. This disruption dysregulates both dopaminergic and noradrenergic systems, providing a mechanistic explanation for core ADHD symptomatology (50).

5. Conclusion

This study identified biochemical abnormalities in Iraqi pediatric patients diagnosed with autism spectrum disorder and attention-deficit/hyperactivity disorder. Key findings included elevated norepinephrine concentrations, which correlate with anxiety and hyperactive manifestations; deficiencies in essential trace elements including zinc, iron, and magnesium, which are critical for optimal neurological function; and increased copper levels, contributing to enhanced oxidative stress. These biochemical alterations suggest multifactorial etiology involving both environmental and physiological components that may exacerbate clinical symptomatology. These findings underscore the necessity for interventional investigations aimed at modulating these biochemical parameters through targeted nutritional supplementation or pharmacological therapeutic strategies.

6. Declarations

6.1 Acknowledgments

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in Thi-Qar Governorate and the Autism Unit at Shatra General Hospital for their valuable assistance in participant recruitment and sample collection. We also acknowledge the technical support provided by the Department of Chemistry, College of Science, University of Thi-Qar in conducting laboratory analyses.

6.2 Ethical Considerations

This study was conducted under the supervision of specialized physicians in Thi-Qar Governorate. Institutional approval was obtained from the Iraqi Ministry of Health/Thi-Qar Health Directorate (Research Committee Approval No. 241 dated November 29, 2023). Additionally, Mission Facilitation Letter No. 801 dated November 29, 2023 authorized research activities at both the Autism Center in Thi-Qar Governorate and Al-Shatra General Hospital. Prior informed consent was obtained from all participating children's parents or legal guardians.

6.3 Authors' Contributions

H.M.K: Conceptualized the study, collected patient and control samples, performed laboratory analyses, and contributed to data interpretation and initial drafting. H.R.F: Assisted in laboratory and statistical analyses, contributed to data interpretation, methodology development, and manuscript editing. T.K.H: Provided samples and clinical resources, supervised medical consultations, ensured sample integrity, contributed to clinical data interpretation, and reviewed the manuscript. The authors read and approved the final manuscript.

6.4 Conflict of Interest

The authors declare no conflict of interest.

6.5 Fund or Financial Support

This research was not funded by any public, commercial, or not-for-profit funding agency.

6.6 Using Artificial Intelligence Tools (AI Tools)

The researchers refrained from employing artificial intelligence instruments.

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