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Cognitive Impairment Profile in Adolescents with Iron Deficiency Anemia: A Comparative Cross-Sectional Analysis

Juraeva Gulkhumor Abbosjon kizi

Master's Degree Student, Department of Pediatrics 2, Fergana Medical Institute of Public Health, Fergana, Uzbekistan E-mail: sardorjuraev0611@gmail.com

Scientific Advisor: PhD Akhmadaliyev Sh. Sh.

ABSTRACT

Iron deficiency anemia (IDA) is a leading nutritional disorder among adolescents globally, with well-documented consequences for brain function and cognitive development. This cross-sectional comparative study investigated characteristics of cognitive impairment in 120 adolescents aged 12-17 years in the Fergana region of Uzbekistan. Sixty adolescents with confirmed IDA were compared with 60 age- and sex-matched healthy controls. Cognitive function was assessed using the Schulte Table Test, Digit Span Task, Stroop Color-Word Test, and Trail Making Test. Adolescents with IDA showed significantly impaired performance across all cognitive domains - sustained attention, working memory, executive function, and processing speed - compared to controls. Anemia severity correlated inversely with cognitive composite scores. Female adolescents were disproportionately affected. These findings highlight the burden of anemia-related cognitive dysfunction in adolescents and support integration of cognitive screening within routine anemia management protocols.

Keywords: *anemia; adolescents; cognition; attention; iron deficiency; neuropsychology; hemoglobin; executive function; memory*

INTRODUCTION

Iron deficiency anemia (IDA) remains one of the most prevalent nutritional disorders worldwide, affecting an estimated 1.62 billion people and representing approximately 24.8% of the global population [1]. Adolescents, particularly female adolescents, constitute one of the highest-risk groups owing to accelerated growth requirements, hormonal changes, and periodic menstrual iron losses [2, 3]. In low- and middle-income countries, the burden is substantially higher, with prevalence rates exceeding 40% in some regions [4]. Regional data from Eastern Europe and Central Asia confirm that adolescent anemia remains a significant public health challenge in Uzbekistan and neighboring countries, where population-level fortification program coverage remains partial [5].

The pathophysiological mechanisms linking IDA to cognitive dysfunction are multifaceted and well-documented. Iron is essential for numerous neurobiological processes, including the myelination of neural pathways, mitochondrial energy metabolism, and the synthesis of critical neurotransmitters such as dopamine and serotonin [6, 7]. Iron deficiency impairs the enzymatic activity of tyrosine hydroxylase and tryptophan hydroxylase, which are responsible for dopamine and serotonin biosynthesis respectively, thereby disrupting the dopaminergic and serotoninergic circuits that govern attention, reward processing, and emotional regulation [8]. Furthermore, chronic iron deficiency has been associated with disrupted myelin protein synthesis and altered dendritic morphology, with potential long-lasting effects on synaptic plasticity and neurodevelopmental milestones [9].

Adolescence represents a critical window for the maturation of executive functions, underpinned by the prefrontal cortex and its subcortical connections [10]. Previous investigations have demonstrated significant associations between IDA and deficits in sustained attention, information processing speed, short-term and working memory, and overall academic performance [2, 11]. A systematic review by Samson et al. reported consistent negative associations between IDA and multiple cognitive domains in adolescents across diverse geographic settings, with preliminary evidence of partial reversibility following iron supplementation [2]. Cognitive deficits have also been observed in adolescents with iron deficiency in the absence of clinical anemia, underscoring the neurocognitive importance of iron status beyond hematological thresholds [8, 18].

Despite accumulating global evidence, data characterizing the specific profile of cognitive impairment in anemic adolescents within Central Asian populations remain scarce. The present study was designed to systematically evaluate and characterize domain-specific cognitive impairments in adolescents with IDA compared to healthy peers in the Fergana region of Uzbekistan, and to examine associations between anemia severity indicators and cognitive performance outcomes.

METHODS

Study Design and Setting

This cross-sectional comparative study was conducted between January 2023 and December 2024 at pediatric outpatient clinics affiliated with the Fergana Medical Institute of Public Health, Uzbekistan. The study protocol received ethical approval from the institutional review board. Written informed consent was obtained from all participants and their legal guardians prior to enrollment.

Participants

A total of 120 adolescents aged 12-17 years were recruited using purposive sampling. The study group comprised 60 adolescents with confirmed IDA, and the control group consisted of 60 age- and sex-matched healthy adolescents without anemia. Inclusion

criteria for the IDA group included: hemoglobin concentration below 12.0 g/dL in females or below 13.0 g/dL in males (per WHO 2011 age- and sex-specific thresholds), serum ferritin below 12 ug/L, and absence of chronic systemic disease. Exclusion criteria included known neurological or psychiatric disorders, intellectual disability, current use of iron supplementation or psychotropic medications, active infectious illness, and any condition independently affecting cognitive function.

Laboratory Assessment

Venous blood samples were collected from all participants under standardized fasting conditions. Hematological parameters - including hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and red cell distribution width (RDW) - were measured using an automated hematology analyzer (Sysmex XN-1000). Serum ferritin was quantified by enzyme-linked immunosorbent assay (ELISA). Anemia severity was classified as mild (Hb 10.0-11.9 g/dL) or moderate (Hb 8.0-9.9 g/dL) per WHO criteria.

Cognitive Assessment

Cognitive function was assessed using a standardized battery of four validated neuropsychological instruments, each targeting a distinct cognitive domain. All tests were administered in the same sequence by a trained clinical psychologist under standardized, distraction-free conditions. The assessment instruments are described in Table 1.

Table 1.

Cognitive assessment instruments used in the study.

Assessment Instrument	Cognitive Domain	Admin. Time	Output Metric	Reliability
Schulte Table Test	Sustained Attention / Processing Speed	5-10 min	Completion time (seconds)	r = 0.83
Digit Span Task (WAIS-IV)	Working Memory	10-15 min	Forward / backward digit span	r = 0.87
Stroop Color-Word Test	Executive Function / Response Inhibition	10 min	Interference score (seconds)	r = 0.79
Trail Making Test (Parts A & B)	Cognitive Flexibility / Processing Speed	5-10 min	Completion time (seconds)	r = 0.85

Note: Reliability coefficients represent test-retest reliability from published validation studies.

Statistical Analysis

All data were analyzed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was applied to assess normality of distribution. Given

the non-normal distribution of cognitive and hematological variables, results are reported as median with interquartile range [Me (IQR)]. Between-group comparisons were performed using the Mann-Whitney U test. Correlations between hemoglobin and serum ferritin values and cognitive performance scores were assessed using Spearman rank correlation coefficients. A two-tailed p-value of <0.05 was considered statistically significant.

RESULTS

Demographic and Hematological Characteristics

The two groups were well-matched in terms of age and sex distribution. The median age was 14.3 years (IQR: 13.0-15.7) in the IDA group and 14.1 years (IQR: 12.9-15.4) in the control group (p = 0.48). Female participants constituted 63.3% of the IDA group and 60.0% of the control group (p = 0.71). All hematological parameters were significantly different between groups. Median hemoglobin in the IDA group was 9.8 g/dL compared to 13.4 g/dL in controls. Median serum ferritin was markedly lower in the IDA group (7.2 ug/L) versus controls (28.6 ug/L). MCV and RDW values were consistent with microcytic anemia. All hematological between-group differences were statistically significant (p < 0.001). The full demographic and hematological profile is presented in Table 2.

Table 2.

Demographic and hematological characteristics of the study groups.

Parameter	IDA Group (n=60)	Control Group (n=60)	p-value
Age (years), Me [IQR]	14.3 [13.0-15.7]	14.1 [12.9-15.4]	0.48
Female, n (%)	38 (63.3%)	36 (60.0%)	0.71
BMI (kg/m2), Me [IQR]	19.4 [17.8-21.2]	20.1 [18.5-21.9]	0.19
Hemoglobin (g/dL), Me [IQR]	9.8 [8.6-11.0]	13.4 [12.8-14.1]	<0.001
Serum Ferritin (ug/L), Me [IQR]	7.2 [5.1-9.8]	28.6 [21.4-36.3]	<0.001
MCV (fL), Me [IQR]	71.3 [68.1-74.8]	85.4 [82.1-88.9]	<0.001
RDW (%), Me [IQR]	16.8 [15.2-18.4]	12.6 [11.9-13.3]	<0.001

Abbreviations: BMI - body mass index; MCV - mean corpuscular volume; RDW - red cell distribution width; Me - median; IQR - interquartile range.

Cognitive Performance Outcomes

Adolescents with IDA demonstrated significantly impaired performance across all four assessed cognitive domains compared to healthy controls (all p < 0.001). Schulte Table completion time - a measure of sustained attention and processing speed - was

substantially prolonged in the IDA group [52.4 sec (IQR: 46.1-59.8)] compared to controls [38.2 sec (IQR: 33.7-43.5)], representing a 37% increase in task duration. Working memory was markedly reduced in adolescents with IDA, as evidenced by both forward digit span (Me = 5.1 vs. 7.4 in controls) and backward digit span (Me = 3.2 vs. 5.6 in controls) scores.

Executive function, measured via the Stroop Color-Word interference paradigm, was significantly compromised in the IDA group [48.7 sec (IQR: 41.2-56.3)] relative to controls [28.4 sec (IQR: 23.6-33.2)], indicating substantially reduced inhibitory control capacity. Trail Making Test completion times - for both the visuomotor sequencing component (Part A) and the cognitive flexibility component (Part B) - were approximately 50-65% longer in the IDA group compared to controls. The overall cognitive composite score was markedly lower in the IDA group [48.6 (IQR: 42.3-55.2)] compared to controls [74.8 (IQR: 68.9-80.5)]. Full cognitive performance data are presented in Table 3.

Table 3.

Cognitive performance outcomes in IDA and control groups.

Cognitive Test	IDA Group, Me [IQR]	Control Group, Me [IQR]	p-value
Schulte Table Time (sec)	52.4 [46.1-59.8]	38.2 [33.7-43.5]	<0.001
Digit Span - Forward	5.1 [4.0-6.0]	7.4 [6.5-8.3]	<0.001
Digit Span - Backward	3.2 [2.5-4.0]	5.6 [4.8-6.5]	<0.001
Stroop Interference (sec)	48.7 [41.2-56.3]	28.4 [23.6-33.2]	<0.001
TMT - Part A (sec)	44.3 [38.5-51.2]	28.1 [24.3-32.6]	<0.001
TMT - Part B (sec)	112.6 [97.4-128.5]	68.4 [59.2-77.8]	<0.001
Cognitive Composite Score*	48.6 [42.3-55.2]	74.8 [68.9-80.5]	<0.001

**Composite score normalized to 100-point scale; higher scores indicate superior performance. Abbreviations: TMT - Trail Making Test; Me - median; IQR - interquartile range.*

Significant inverse correlations were identified between hemoglobin concentration and Schulte Table completion time ($r_s = -0.61$, $p < 0.001$), Stroop interference score ($r_s = -0.54$, $p < 0.001$), and TMT-B time ($r_s = -0.58$, $p < 0.001$), confirming that lower hemoglobin levels were associated with worse cognitive performance. Serum ferritin showed a positive correlation with forward digit span ($r_s = 0.49$, $p < 0.001$) and backward digit span scores ($r_s = 0.52$, $p < 0.001$). Adolescents with moderate anemia (Hb 8.0-9.9 g/dL) exhibited the most pronounced deficits, particularly in executive function and working memory, compared to those with mild anemia (Hb 10.0-11.9

g/dL). Within the IDA group, female adolescents showed significantly lower backward digit span scores than male counterparts (Me = 2.8 vs. 3.9, p = 0.03). Figure 1 illustrates the domain-specific cognitive performance profile across both groups.

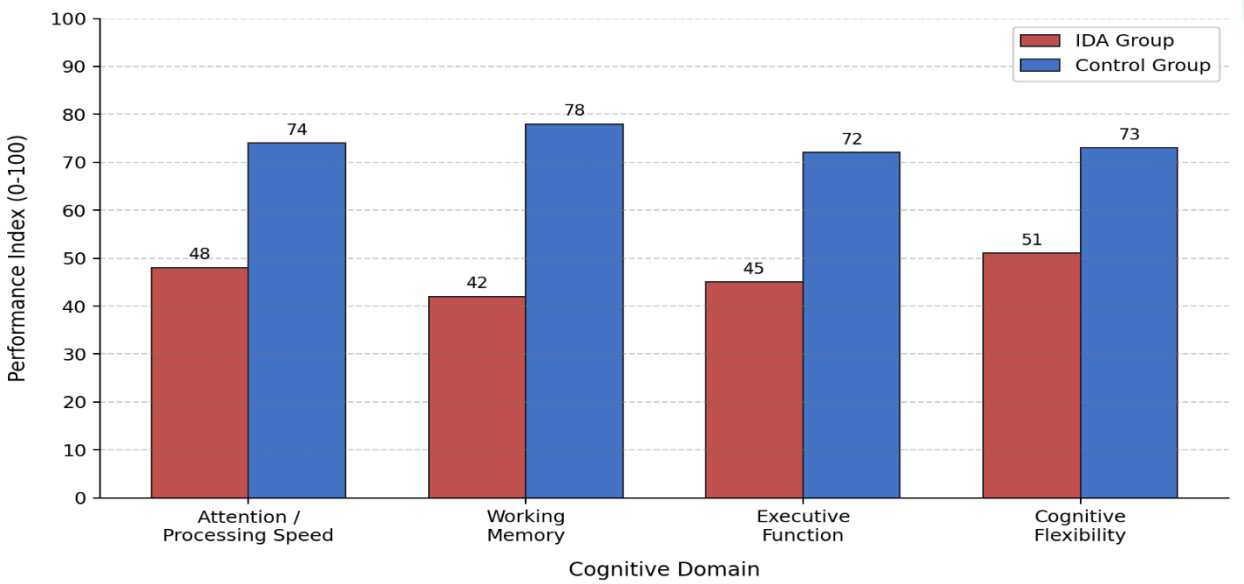

Figure 1. *Domain-specific cognitive performance index scores (0-100) in adolescents with IDA versus healthy controls. Higher scores indicate superior performance. All between-group differences were statistically significant ($p < 0.001$).*

DISCUSSION

The present study demonstrates a clear, statistically significant, and clinically meaningful pattern of cognitive impairment across multiple domains in adolescents with IDA compared to healthy matched controls. The affected domains - sustained attention, working memory, processing speed, and executive function - collectively represent the core neurocognitive architecture underlying academic learning and adaptive daily functioning. These findings are broadly consistent with the global literature [2, 3, 11] while providing specific population-level evidence from a Central Asian clinical setting.

The neurobiological basis for these observations is well-established. Iron is an indispensable cofactor for tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis [6, 12]. Reduced dopaminergic signaling in the prefrontal-striatal circuits is recognized as a central mechanism underlying attentional instability, impulsivity, and working memory dysfunction in iron-deficient individuals [9, 13]. The consistent and prominent impairment of working memory observed in our IDA cohort - reflected in both forward and backward digit span deficits - is consistent with this proposed mechanism. Iron also participates in the synthesis of myelin basic proteins; deficits in myelination are associated with slowed neural conduction, directly manifesting as

prolonged processing speeds [7, 14]. This mechanistic link explains the significantly extended Schulte Table and TMT completion times observed in the IDA group.

The dose-response relationship between hemoglobin concentration and cognitive performance, evidenced by robust negative Spearman correlations, aligns with prior investigations. Murray-Kolb and Beard demonstrated that iron repletion in young women normalized cognitive functioning, particularly in tests of attention and memory [13]. Similarly, Bruner et al. reported improvements in attention and memory following iron supplementation in non-anemic iron-deficient adolescent girls, emphasizing that the cognitive burden extends to iron deficiency states preceding frank anemia [15]. A recent meta-analysis by Fiani et al. further confirmed these patterns, documenting significant associations between iron status and cognitive outcomes independent of anemia severity [8].

The disproportionate cognitive burden observed in female adolescents is consistent with established epidemiological patterns. Menstrual iron losses compound the nutritional vulnerability already imposed by growth-related demands, particularly in settings where dietary iron intake and supplementation coverage remain suboptimal [5, 16]. In Central Asia, regional data confirm that fortification programs in Uzbekistan cover approximately 40-50% of the population, leaving a substantial proportion of adolescent girls at persistent nutritional risk [5]. The strong association between moderate anemia severity and cognitive deficits in our study underscores the urgency of timely and adequate therapeutic intervention.

The observed deficits in backward digit span - a task sensitive to prefrontal lobe integrity and executive working memory - are particularly noteworthy from an educational perspective. Working memory capacity is a strong predictor of academic achievement across diverse subjects and age groups [19]. Sustained attentional deficits, as reflected in prolonged Schulte Table performance, are associated with difficulties in classroom learning, reading comprehension, and mathematical reasoning [17]. The aggregate cognitive burden observed in the IDA group therefore has direct implications for educational outcomes in a region where adolescent academic performance is a key development priority.

Several limitations warrant acknowledgment. The cross-sectional design does not permit causal inference and reverse causality cannot be excluded. The single-region recruitment limits generalizability. Dietary intake, socioeconomic status, and formal educational attainment were not systematically controlled as potential confounders. Longitudinal studies incorporating post-supplementation cognitive reassessment are necessary to establish causality and evaluate the extent of cognitive reversibility following adequate iron therapy.

CONCLUSION

Adolescents with iron deficiency anemia present a distinct and measurable profile of cognitive impairment encompassing sustained attention, working memory, processing speed, and executive function - domains fundamental to academic achievement and adaptive daily functioning. The severity of cognitive deficits correlates with the degree of anemia, and female adolescents bear a disproportionate burden. These findings compellingly demonstrate that IDA is not merely a hematological condition but a neurodevelopmental challenge with far-reaching consequences for intellectual capacity and quality of life. Healthcare systems in regions of high anemia prevalence, including Central Asia, should urgently integrate cognitive screening within routine anemia management protocols for adolescents. Early identification of IDA, paired with timely iron therapy and educational support, represents the most promising strategy to protect and restore the cognitive potential of this vulnerable and vital population.

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