Cognitive and Peripheral Nerve Function Impairment in Iron Deficiency Anemia: Association with Serum Ferritin Levels in Adults

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KEYWORDS

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ABSTRACT

Background: Iron deficiency anemia (IDA) is a global health concern with potential cognitive and neurological consequences. Iron is essential for neuronal myelination, neurotransmitter synthesis, and oxygen transport to the brain. This study investigates the relationship between iron deficiency and neurocognitive function in adults.**Aim:** To evaluate the correlation between serum ferritin levels and both cognitive function (measured by Montreal Cognitive Assessment [MoCA]) and peripheral nerve function (measured by Nerve Conduction Velocity [NCV]) in adults with iron deficiency anemia.**Methods:** This cross-sectional study included 134 participants (67 newly diagnosed untreated IDA cases and 67 healthy controls) aged 20-40 years recruited from a rural hospital in eastern Uttar Pradesh, India. Participants underwent complete blood count, serum ferritin measurement, MoCA testing for cognitive assessment, and NCV studies for peripheral nerve function evaluation. Statistical analysis included independent t-tests for group comparisons and Pearson's correlation coefficient to assess relationships between serum ferritin and neurocognitive parameters.**Results:** IDA participants showed significantly lower hemoglobin (9.2±2.1 vs. 12.9±0.9 g/dL, $p<0.0001$) and serum ferritin levels (8.87±2.34 vs. 24.21±4.97 ng/mL, $p<0.0001$) compared to controls. Significant impairments were observed in both motor and sensory nerve conduction parameters in IDA cases, with decreased MNCV (29.2±12.7 vs. 55.93±1.4 m/s, $p<0.0001$) and SNCV (36.05±13.9 vs. 24.29±4.9 m/s, $p<0.0001$). Though correlations between serum ferritin and neurocognitive measures did not reach statistical significance, positive trends were observed.**Conclusion:** While no statistically significant correlation was established between serum ferritin levels and neurocognitive function, the significant differences in MoCA scores and NCV parameters between IDA cases and controls suggest that iron deficiency may adversely affect both cognitive and peripheral nerve function. Early screening and management of IDA are recommended to potentially prevent neurological complications.

Introduction

Iron deficiency anemia (IDA) represents a significant global health challenge with implications extending beyond hematological parameters to neurological and cognitive function. Iron plays a fundamental role in numerous physiological processes critical to neuronal health, including oxygen transport, DNA synthesis, neurotransmitter metabolism, and myelination of nerves (Beard, 2001). The relationship between iron status and neurocognitive function has gained increasing attention as evidence suggests that iron deficiency may impair both central and peripheral nervous system function, even before the development of frank anemia (Lozoff et al., 2006).

The burden of IDA is particularly pronounced in India, where the National Family Health Survey (NFHS-5) reports that over 50% of women and children are affected (NFHS-5, 2020-21). This high prevalence is concerning given the potential neurological implications. Indian studies have demonstrated that individuals with IDA perform poorly on cognitive assessments and exhibit reduced nerve conduction velocities, suggesting significant impacts on both central and peripheral nervous systems (Kapoor & Dhillon, 2021). Rural populations, who often have limited access to healthcare resources, show higher prevalence rates and more severe neurological deficits related to iron deficiency (Gupta et al., 2022).

The Montreal Cognitive Assessment (MoCA) has emerged as a valuable tool for evaluating cognitive function across various domains, including attention, memory, language, and executive function (Nasreddine et al., 2005). These cognitive domains are potentially vulnerable in individuals with compromised iron status. Similarly, Nerve Conduction Velocity (NCV) studies provide critical information about peripheral nerve function, detecting abnormalities such as demyelination and axonal degeneration that may result from nutritional deficiencies including iron deficiency (Yücel et al., 2003).

Despite growing evidence suggesting a link between iron status and neurological function, there remains a significant gap in understanding the precise relationship between serum ferritin levels (a marker of iron stores) and specific neurocognitive parameters in adults with IDA. Most existing studies have focused on children or pregnant women, leaving the adult population, particularly in rural settings, understudied.

This research aims to address this knowledge gap by investigating the correlation between serum ferritin levels and both cognitive function (assessed using MoCA) and peripheral nerve function (measured using NCV) in adults with IDA. By elucidating these relationships, this study seeks to contribute to a more comprehensive understanding of IDA's neurological consequences and emphasize the importance of early detection and management to mitigate potential neurocognitive effects.

Materials and Methods

Study Design and Setting

This cross-sectional study was conducted in the Departments of Physiology and Psychiatry at Government Medical College and associated teaching hospital in Kannauj, Uttar Pradesh, India. The study site primarily serves rural populations from surrounding areas.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee of Institute. Written informed consent was obtained from all participants after explaining the study procedures in their native language. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Study Population

The study enrolled 134 participants, comprising 67 cases with newly diagnosed untreated IDA and 67 healthy controls. Participants were predominantly from low socioeconomic backgrounds who visited the Medicine Outpatient Department for various acute illnesses.

Inclusion Criteria

- Age 20-40 years
- Newly diagnosed cases of IDA who had not received any treatment
- Willing to participate and provide informed consent

Exclusion Criteria

- History of chronic illnesses such as diabetes mellitus, thyroid disorders, or renal disease
- Neurological disorders or peripheral neuropathy from any other cause
- History of alcoholism or substance abuse
- Pregnancy or lactation
- Current use of medications known to affect cognitive function or peripheral nerve conduction
- Inability to perform cognitive tests due to language barriers or illiteracy

Sample Size Calculation

The sample size was calculated using the formula for comparative studies, assuming a 5% level of significance, 80% power, and an anticipated minimum correlation coefficient of 0.3 between serum ferritin and neurocognitive parameters based on previous studies. The calculated sample size was 64 participants per group, which was rounded to 67 to account for potential data loss.

Data Collection

Clinical Assessment

A comprehensive clinical examination and detailed history were obtained from all participants. Demographic information including age, gender, education level, occupation, socioeconomic status, and dietary habits was recorded using a structured questionnaire.

Laboratory Assessments

Blood samples were collected from all participants after overnight fasting. Complete blood count was performed using Swelab Alfa Plus 3-part hematology analyzer (Boule Diagnostics, Sweden). The diagnosis of IDA was based on the following criteria:

- Hemoglobin (Hb) < 13 g/dL in males and < 12 g/dL in females
- Mean Corpuscular Volume (MCV) < 80 fL
- Mean Corpuscular Hemoglobin (MCH) < 27 pg
- Mean Corpuscular Hemoglobin Concentration (MCHC) < 31 g/dL

Serum ferritin levels were measured using an Immunoassay analyzer (Beckman Coulter Access 2, USA). Serum ferritin < 15 ng/mL was considered indicative of iron deficiency.

Nerve Conduction Studies

Nerve conduction studies were performed using the Neurostim machine (Medicaid Systems, Chandigarh, India) at a controlled room temperature of 22-24°C. Three disc surface electrodes were used: recording electrode, reference electrode, and ground electrode. Conductive gel was applied to reduce impedance between the electrodes and skin.

For the right median nerve, both motor and sensory nerve conduction studies were performed. The following parameters were measured:

- Motor nerve: Distal latency (DL), Compound Muscle Action Potential (CMAP) amplitude, and Motor Nerve Conduction Velocity (MNCV)
- Sensory nerve: Distal latency (DL), Sensory Nerve Action Potential (SNAP) amplitude, and Sensory Nerve Conduction Velocity (SNCV)

Cognitive Assessment

Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) in the participant's native language. The MoCA evaluates various cognitive domains including attention, concentration, executive function, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The maximum score is 30 points, with a score ≥ 26 considered normal.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics (Version 25.0, IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation (SD). The normality of data distribution was tested using the Shapiro-Wilk test. Independent samples t-test was used to compare means between the two groups. Pearson's correlation coefficient was calculated to assess the relationship between serum ferritin levels and neurocognitive parameters (MoCA scores and NCV parameters). A p-value < 0.05 was considered statistically significant.

Results

Demographic Characteristics

The study included 134 participants (67 cases and 67 controls) with a mean age of 33.0 ± 7.0 years for cases and 30.0 ± 4.8 years for controls. The case group comprised 17 males (25.37%) and 50 females (74.63%), while the control group included 23 males (34.33%) and 44 females (65.67%). The majority of participants (79.10% of cases and 77.61% of controls) were in the 26-40 years age group. There were no statistically significant differences in height and weight between cases and controls (Table 1).

Table 1: Demographic characteristics of the study participants

Demographic characteristics	**Cases**	**Percentage**	**Control**	**Percentage**
Gender				
Male	17	25.37%	23	34.33%
Female	50	74.63%	44	65.67%
Age group				
20-22	09	13.43%	03	4.48%
23-25	05	7.46%	12	17.91%
26-40	53	79.10%	52	77.61%
Height (cm)	154.74±7.44		156.18±7.06	
Weight (Kg)	56.16±10.09		58.46±9.42	

Hematological Parameters

Participants with IDA had significantly lower hemoglobin levels (9.2 ± 2.1 g/dL) compared to controls (12.9 ± 0.9 g/dL, p < 0.0001). Similarly, serum ferritin levels were significantly reduced in the IDA group (8.87 ± 2.34 ng/mL) compared to the control group (24.21 ± 4.97 ng/mL, p < 0.0001) (Table 2).

Table 2: Comparison of hematological parameters between cases and controls

Parameters	**Cases**	**Control**	**t-statistic**	**P- value**
Hemoglobin	9.2±2.1	12.9±0.9	13.25	<0.0001
S. ferretin	8.87±2.34	24.21±4.97	22.85	<0.0001

Nerve Conduction Parameters

Motor nerve conduction studies of the right median nerve revealed significant differences between cases and controls. The IDA group showed prolonged distal latency (5.5 ± 2.0 ms vs. 4.4 ± 0.3 ms, $p < 0.0001$), reduced CMAP amplitude (9.77 ± 7.6 mV vs. 14.5 ± 0.6 mV, $p < 0.0001$), and decreased MNCV (29.2 ± 12.7 m/s vs. 55.93 ± 1.4 m/s, $p < 0.0001$) compared to controls (Table 3).

Table 3: Comparison of motor nerve conduction parameters of right median nerve

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Nerve	**Parameters**	**Mean**±SD		**t-statistic**	**P-value**
		Cases	**Control**		
Right median nerve	DL (sec)	5.5±2.0	4.4±0.3	-4.452	<0.0001
	CMAP (mV)	9.77±7.6	14.5±0.6	-5.079	<0.0001
	MNCV (m/s)	29.2±12.7	55.93±1.4	17.124	<0.0001

Similarly, sensory nerve conduction studies showed significant abnormalities in the IDA group. Cases exhibited prolonged distal latency (5.9 ± 3.2 ms vs. 3.03 ± 0.28 ms, $p < 0.0001$), reduced SNAP amplitude (9.77 ± 3.17 µV vs. 15.75 ± 1.8 µV, $p < 0.0001$), and altered SNCV (36.05 ± 13.9 m/s vs. 24.29 ± 4.9 m/s, $p < 0.0001$) compared to controls (Table 4).

Table 4: Comparison of sensory nerve conduction parameters of right median nerve

Nerve	**Parameters**	**Mean**±SD		**t-statistic**	**P-value**
		Cases	**Control**		
Right median nerve	DL (sec)	5.9±3.2	3.03±0.28	-7.313	<0.0001
	CMAP (mV)	9.77±3.17	15.75±1.8	13.427	<0.0001
	SNCV (m/s)	36.05±13.9	24.29±4.9	-6.832	<0.0001

Montreal Cognitive Assessment (MoCA) Scores

The mean MoCA score was significantly lower in the IDA group (22.4 ± 3.2) compared to the control group (27.3 ± 1.6, $p < 0.0001$), indicating impaired cognitive function in participants with iron deficiency anemia.

Correlation Analysis

Correlation analysis between serum ferritin levels and neurocognitive parameters showed non-significant but potentially meaningful trends (Table 5). A very small positive correlation was observed between serum ferritin and SNCV ($r = 0.067$, $p = 0.590$), while a very small negative correlation was found with MNCV ($r = -0.073$, $p = 0.559$). The correlation between MoCA scores and nerve conduction parameters showed non-significant but positive trends with both SNCV ($r = 0.214$, $p = 0.082$) and MNCV ($r = 0.189$, $p = 0.125$).

Table 5: Correlation analysis between serum ferritin, nerve conduction parameters, and MoCA scores in cases

Table 5:				
Correlation	S. ferretin	SNCV	MNCV	MOCA score
Pearson coefficient (r)	0.067	-0.073	0.214	0.189
R^2	0.045	0.005	0.045	0.035
P value	0.590	0.559	0.082	0.125
T statistic	-0.540	-0.587	1.763	1.551

Note: SNCV = Sensory Nerve Conduction Velocity; MNCV = Motor Nerve Conduction Velocity; MoCA = Montreal Cognitive Assessment

Discussion

This study investigated the relationship between iron deficiency anemia and neurocognitive function in adults, focusing on the correlation between serum ferritin levels and both cognitive performance and peripheral nerve function. The findings reveal significant differences in nerve conduction parameters and cognitive scores between individuals with IDA and healthy controls, though the direct correlation between serum ferritin and these neurocognitive measures did not reach statistical significance.

Cognitive Function in Iron Deficiency Anemia

Our findings of lower MoCA scores in the IDA group align with growing evidence that iron deficiency can adversely affect cognitive function. The MoCA, designed by Nasreddine et al. (2005) to detect mild cognitive impairment, effectively captured the cognitive differences between our study groups. The observed cognitive impairment in IDA may be attributed to iron's crucial role in neurotransmitter synthesis, myelination, and neural metabolism (Beard, 2001). Even mild iron deficiency can impact multiple cognitive domains, including attention, memory, and executive function.

These results are consistent with previous research by Bruner et al. (1996), who demonstrated significant improvements in cognitive function following iron supplementation in adolescents with non-anemic iron deficiency. Similarly, a study by Kapoor and Dhillon (2021) among Indian adults showed that iron deficiency was associated with poorer performance on cognitive assessments, particularly affecting attention and processing speed.

The lack of a statistically significant correlation between serum ferritin levels and MoCA scores in our study, despite the clear group differences, suggests that the relationship between iron status and cognitive function may be complex and potentially influenced by factors beyond absolute iron levels. These factors might include the duration of iron deficiency, individual compensatory mechanisms, or the presence of other micronutrient deficiencies that commonly co-exist with iron deficiency.

Peripheral Nerve Function in Iron Deficiency Anemia

The significant alterations in both motor and sensory nerve conduction parameters in our IDA group are consistent with previous studies demonstrating the impact of iron deficiency on the peripheral nervous system. The prolonged distal latencies, reduced amplitudes, and altered conduction velocities observed in participants with IDA suggest that iron deficiency may affect both myelin integrity and axonal function.

These findings parallel those of Yücel et al. (2003), who reported delayed motor and sensory conduction velocities in infants with IDA, and Park et al. (2018), who observed significant neurological symptoms and abnormal NCV in adults with chronic iron deficiency. Our study extends these observations by documenting similar neurophysiological changes in a rural Indian adult population, suggesting that the neurological consequences of IDA are not limited to developmental stages but can manifest or persist into adulthood.

The mechanisms underlying these neurophysiological changes likely involve iron's role in myelin synthesis and energy metabolism in peripheral nerves. Iron is an essential cofactor for enzymes involved in lipid synthesis, which is crucial for myelin formation and maintenance. Additionally, iron deficiency may impair mitochondrial function in nerve cells, compromising energy production necessary for optimal neural signaling (Beard, 2001; Lozoff et al., 2006).

Clinical and Public Health Implications

The high prevalence of IDA in our predominantly rural sample underscores a significant public health concern, particularly in resource-limited settings. The World Health Organization emphasizes the importance of addressing nutritional deficiencies to improve overall health outcomes, and our findings further highlight the potential neurological and cognitive benefits of addressing iron deficiency.

The observed neurocognitive impairments in IDA suggest that routine assessment of cognitive function and peripheral nerve status may be valuable in the comprehensive management of patients with iron deficiency. Early identification and treatment of IDA could potentially prevent or mitigate these neurological complications, improving quality of life and functional capacity.

Public health interventions targeting iron deficiency should consider not only the hematological manifestations but also the potential neurocognitive benefits of iron repletion. Bhatia and Gupta (2020) suggested that targeted nutritional interventions in high-risk populations could significantly reduce the burden of anemia and its associated complications, including neurological effects.

Limitations and Future Directions

Despite providing valuable insights, our study has several limitations. The cross-sectional design limits causal inferences, and the relatively small sample size from a specific geographical region may affect the generalizability of our findings. Additionally, we did not assess the duration of iron deficiency, which might influence the extent of neurocognitive impact.

The absence of statistically significant correlations between serum ferritin and neurocognitive parameters, despite clear group differences, warrants further investigation. Future studies should consider:

1. Longitudinal designs to evaluate the temporal relationship between iron status and neurocognitive function
2. Larger, more diverse study populations to improve generalizability
3. Comprehensive assessment of iron status using multiple biomarkers (e.g., transferrin saturation, soluble transferrin receptor)
4. Evaluation of the reversibility of neurocognitive deficits following iron supplementation
5. Investigation of potential molecular mechanisms underlying the observed neurophysiological changes
6. Assessment of other potential contributing factors, such as vitamin deficiencies and inflammatory markers

Additionally, exploring the dose-response relationship between iron status and neurocognitive parameters could provide valuable insights for establishing therapeutic targets and optimizing treatment strategies.

Conclusion

This study demonstrates significant differences in cognitive function and peripheral nerve conduction parameters between adults with iron deficiency anemia and healthy controls. While we did not establish a statistically significant correlation between serum ferritin levels and neurocognitive measures, the observed trends suggest a potential relationship that warrants further investigation.

These findings highlight the importance of considering the neurological and cognitive aspects of iron deficiency anemia in clinical practice. Routine screening for iron deficiency, particularly in high-risk populations, could help identify individuals at risk for neurocognitive impairments.

Early intervention with iron supplementation may potentially prevent or ameliorate these complications, though further research is needed to confirm this.

Future studies should focus on elucidating the mechanisms underlying the neurocognitive effects of iron deficiency and evaluating the impact of iron supplementation on reversing these deficits. A better understanding of these relationships could inform more comprehensive approaches to managing iron deficiency anemia and its multisystem consequences.

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Conflicts of Interest

The authors declare no conflicts of interest.

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