

Looking Through a Crystal. Ball: Impact of iron status on Cognitive Functions in Egyptian Children

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Original
Article

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ABSTRACT

Objective: Determine the effect of iron deficiency anemia (IDA) & iron deficiency (ID), on the cognitive functions in children and its consequences.

Patients and Methods: Three groups of children were enrolled in this case-control study with an age range of 3- 8 years. They were selected from pediatric and phoniatic clinics in Egypt. Control group (CG): thirty normal children. Case groups were divided into Group I: Nineteen Delayed language development children had ID only, Group II: Thirty Delayed language development children had iron deficiency anemia (IDA). Groups were subjected to (1) Full history taking (focusing on nutritional history). (2) CBC by automatic cell counters. (3) Iron status through estimation of serum ferritin level by ELISA. (4) Assessment of cognitive functions by assessment of Non- verbal Intelligent Quotient (NV-IQ) using Stanford Binet 5th Edition measuring (fluid reasoning, knowledge, quantitative reasoning, visual-spatial processing, and working memory). (5) Assessment of language-by-language test to confirm diagnosis of delayed language development.

Results: Under the umbrella of faulty eating habits, there was a direct correlation between the NV-IQ and the deterioration of iron status with their consequence on delaying language development.

Conclusion: There is a necessary to assess NV-IQ and iron status in any child with delayed language development with poor attention span, intelligence, sensory perception functions, emotions, and behavior, especially with the condition of faulty eating habits.

Key Words: Cognition, cognitive function, iron-deficiency anemia, non - verbal-Intelligent Quotient.

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INTRODUCTION

The cognitive impairment and behavioral changes were caused by micronutrient deficiencies in the perinatal period and childhood^[1]; micronutrients have an essential role in the proper myelination of dendrocytes (visual, auditory) the sensory systems. Visuomotor development and general cognitive disturbances were related to (ID)^[2]. Attention span, intelligence, sensory perception functions, emotions, and behavior were linked to mitochondrial brain damage due to ID^[3]. Golub et al. showed that rhesus monkeys had impaired neurologic function at birth due to inadequate intake of iron from the diet during pregnancy^[4].

Dietary iron could be found as non-heme iron and heme iron. The absorption of iron in those two forms are different. Non-heme iron can be found either reduced or oxidized. This absorption is maximized by ascorbic acid but is inhibited by phytates, calcium, and polyphenols^[5].

Thang & Shanthy considered that eighty percent of children aged between five and ten years had IDA^[6]. 5th report on the world nutrition situation reported that anemia, especially IDA causes maternal deaths and cognitive deficits in young children worldwide^[7]. The motor performances differ significantly between anemic and non-anemic children^[8].

Nutrition is the cornerstone for the growth of the brain, language, and cognitive development^[9]. Therefore, studying the effect of ID and IDA on NV-IQ as a mirror to cognitive brain function is the concern of this study.

2. Objectives:

Determine the effect of IDA & ID on the cognitive functions in children and its consequences.

PATIENTS AND METHODS:

3.1 Participant:

The study was done on seventy-nine children in our faculty. The children were chosen according to the inclusion and exclusion criteria. All parents agreed to undergo the assessment and had formal consent.

Seventy-nine children were enrolled in this case-control study with the age range of 3 - 8 years, including a control group: thirty normal children with normal CBC and iron profiles. The study groups had delayed language development children divided into two groups: Group I: Nineteen children had iron deficiency (ID) only (i.e., serum ferritin below 20 and normal CBC parameters), Group II: Thirty children had IDA (i.e., serum ferritin below 20 and abnormal CBC parameters). CBC parameters cutoff values as following: Hb < mean (12 gm/dl), Hematocrit < Mean (37%), MCV < (70-74) fl & Ferritin below 20 indicate low iron stores.

All studied children were selected from the pediatric and phoniatric clinics.

3.1.1. Inclusion criteria

- 1- Control group matched in age with studied groups.
- 2- The Control group is healthy children with normal development of language, and their CBC parameters are normal.
- 3- The studied groups were diagnosed previously as Delayed Language Development.
- 4- Their native language is Arabic, and their age ranged between 3 and 8 years old.
- 5- C-reactive protein is below five (quantitative) or negative (qualitative) for both study and control groups.

3.1.2. Exclusion criteria:

- 1- Any secondary cause of delayed language development.
- 2- Any family history of language or speech disorders.
- 3- Any hematological disease.
- 4- Any other pediatric disorders

3.2. Assessment:

All studied groups were subjected for the following:

3.2.1. History

A detailed history was taken, including:

- A) Personal and family to exclude the hereditary factor.

- B) Full pediatric evaluation (focusing on nutritional history).

- C) Complete phoniatric evaluation to confirm diagnosis of delayed language development (a phoniatrician carried language evaluation to determine the passive language skills and the active language spoken).

3.2.2. Procedures:

- 1- CBC by automatic cell counters, that is, Coulter for hemoglobin concentration.
- 2- Iron status by estimating serum ferritin level by ELISA.
- 3- Estimated C reactive protein (CRP) by ELISA, serum ferritin is an acute-phase CRP reaction.

So, measuring the serum ferritin level to exclude inflammation or infection, increasing acute phase reactant. CRP is negative in qualitative measures or below five in quantitative measures.

- 4- The non-verbal Stanford-Binet Intelligence Scale 5th edition (SB-5th)^[10] is an individually administered test for cognitive ability from 2 to 85 years. The five factors (NV-IQ) measured were: Fluid Reasoning, Knowledge, Quantitative Reasoning, Working Memory, and Visual-Spatial Reasoning. Scores are classified as follows: Very gifted (145–160), Gifted (130–144), Superior (120–129), High average (110–119), Average (90–109), Low average (80–89), Borderline impaired (70–79), Mild MR (55–69), Moderately MR (40–54).

Statistical Analysis:

SPSS 24 was done on the tabulated data. We use One-Sample Kolmogorov - Smirnov to evaluate normal distribution parameters. Frequencies and percentages were used for qualitative data by Chi-square and Fisher's exact tests. The means and standard deviations (SDs) presented the quantitative data by measuring the difference between more than two study group means for parametric data by One-Way ANOVA test rather than non-parametric data were used Kruskal-Wallis test. *P values* ≤ 0.05 indicate significance.

RESULTS:

(a)- Descriptive statistics:

The current work was a case-control study that included seventy - nine Egyptian children (48 (60.8%) males and 31 (39.2%) females) previously diagnosed (during the last three months) with DLD (using language test; their language age was below their chronological age). The sample was taken in the period between February 2021 and April 2021. Their ages ranged from 3 years and 1 month to 8 years. There were non-significant statistical differences between female

mean ages. Case Groups were divided into Group1: (iron deficiency (ID)); 19 patients (12 males, seven females), with a mean age (5 ± 1.4 years). Control group: (non-anemic control group); 30 patients (21 boys, nine girls), with a mean age (6.1 ± 1.3 years). Group2: (iron deficiency anemia (IDA)); 30 patients (15 males, 15 females), with mean age (5.4 ± 1.6). Demographic characteristics of the (Table 1).

Table (1): Socio-demographic data of all groups

(b)- Comparative statistics:

Table (2): Correlation between (ID & IDA) and control (non-anemic children) regarding blood indices.

Table (3a): Correlation between the control group and both studying groups (ID & IDA) according to non-verbal items of Stanford Binet fifth edition and total score.

Table (3b): Correlation between the control and study groups (ID & IDA) according to Visual-Spatial.

Table (4): Distribution between the degree of total non-verbal IQ and its sub-items among control and ID.

Table (5): Distribution between the degree of total non-verbal IQ and its sub-items among control and IDA.

Table (6): Distribution and comparison between degree of total non-verbal IQ and its sub-items among IDA and ID.

Table 1: Socio demographic data of the studied groups

	Group	N	Mean	SD	Median	Range
Age	Control	30	6.1	1.3	6.1	3.6-8
	ID	19	5.0	1.4	4.6	3.3-7.8
	IDA	30	5.4	1.6	5.2	3.1-8
	Group	Male (n=48)	Female (n=31)	Total (n=79)	X ²	P Value
Gender	Control	21 (43.8%)	9 (29.0%)	30 (38.0%)	2.58 ^b	0.274
	ID	12 (25.0%)	7 (22.6%)	19 (24.1%)		
	IDA	15 (31.3%)	15 (48.4%)	30 (38.0%)		

Chi-Square Test, $p > 0.05$.

(b)-Comparative statistics:

Table 2: Correlation between (ID & IDA) and control (non-anemic children) regarding to blood indices.

	group	Mean	SD	Median	F	P Value	Sig.
Hb mean(12gm/dl)	Control ^{a,b}	12.6	0.5	12.7	166.59	<0.001	HS
	ID ^{b,a}	12.9	0.8	12.9			
	IDA ^c	9.5	0.9	9.9			
Hematocrite Mean(37%)	Control	34.3	3.1	33.5	0.36	0.697	NS
	ID	33.9	2.7	33.0			
	IDA	33.6	2.8	33.4			
Ferritin	Control ^a	43.9	17.6	40.0	64.92	<0.001	HS
	ID ^{b,c}	15.5	3.2	17.0			
	IDA ^{c,b}	14.0	3.0	14.0			
RBC _s count	Control	3.7	0.5	3.7	1.05	0.355	NS
	ID	3.5	0.4	3.5			
	IDA	3.8	0.7	3.5			
MCV (70-74fl)	Control ^{a,b}	74.6	1.8	74.0	99.65	<0.001	HS
	ID ^{b,a}	72.2	2.6	72.0			
	IDA ^c	60.0	6.2	62.0			

One-Way ANOVA

The correlation between variable blood indices among control, ID & IDA, revealed that Hb is highly significant difference in IDA rather than control group and iron deficiency group, Ferritin is highly significant difference between control group and study group as mean if ferritin logically high in control group & MCV had highly correlation significance difference in IDA rather than ID group and control group. In contrast the hematocrit and RBCs count showed non significance correlation.

HB = hemoglobin, MCV = Mean Corpuscular volume, fl = femtoliters.

Ferritin below 20 indicate low iron stores.

Table 3a: Correlation between control group and both studying groups (ID&IDA) according to non-verbal items of Stanford Binet fifth edition and total score

	group	Mean	SD	Median	F	P Value	Sig.
Total-IQ	Control ^a	97.6	9.8	100.5	25.64	<0.001	HS
	ID ^b	88.7	7.9	87.0			
	IDA ^c	76.8	14.0	78.0			
Fluid reasoning	Control ^a	103.8	12.8	103.0	17.99	<0.001	HS
	ID ^b	92.9	13.0	96.0			
	IDA ^c	80.3	18.4	78.0			
Knowledge	Control ^{a,b}	94.6	9.2	97.0	13.8	<0.001	HS
	ID ^{b,a}	90.5	10.7	86.0			
	IDA ^c	78.7	14.9	82.5			
Quantitative Reasoning	Control ^a	99.3	9.3	98.0	15.60	<0.001	HS
	ID ^{b,c}	87.9	12.5	89.0			
	IDA ^{c,b}	80.6	16.2	85.0			
Working Memory	Control ^a	95.8	8.7	94.0	24.34	<0.001	HS
	ID ^b	83.6	9.3	84.0			
	IDA ^c	75.5	14.3	77.5			

One-Way ANOVA

There were statistically highly significant differences between control and ID & IDA groups regards Total-IQ, Fluid reasoning, Knowledge & Working Memory. All of them were parametric items. According to Total-IQ, Fluid reasoning & Working Memory, three were highly significance difference between the three groups. In Knowledge item, there were affected in IDA rather than other groups and highly significance difference. In Quantitative Reasoning, there were highly significance difference between studying groups and control group and more affected in IDA more than ID group.

Table 3b: Correlation between control group and both studying groups (ID & IDA) according to Visual-Spatial reasoning

	group	Mean	SD	Median	Range		Visual- Spatial reasoning(VS)	P Value	Sig.
					Min.	Max.			
Visual-Spatial reasoning	Control ^a	99.2	9.0	100.0	78.0	112.0	19.43	<0.001	HS
	ID ^b	92.2	10.2	95.0	78.0	109.0			
	IDA ^c	105.7	129.4	81.5	56.0	787.0			

Kruskal-Wallis Test

This item was non- parametric item. There were statistically highly significant differences between the studied groups , although all of them were average mean.

Table 4: Distribution between degree of total non -verbal IQ and its subitems among control and ID

		Moderate	mild	borderline	Below average	average	High average	X ²	P value
Fluid Reasoning	Control	0	0	1 (3.3%)	6 (20.0%)	13 (43.3%)	10 (33.3%)	5.77	0.113 NS
	ID	0	0	4 (22.2%)	4 (22.2%)	8 (44.4%)	2 (11.1%)		
Knowledge	Control	0	0	0	11 (36.7%)	18 (60.0%)	1 (3.3%)	4.29	0.182 NS
	ID	0	0	2 (10.5%)	9 (47.4%)	8 (42.1%)	0		
Quantitative Reasoning	Control	0	0	0	6 (20.0%)	17 (56.7%)	7 (23.3%)	12.26	0.006 HS
	ID	0	4 (21.1%)	1 (5.3%)	5 (26.3%)	9 (47.4%)	0		
Working Memory	Control	0	0	0	8 (26.7%)	19 (63.3%)	3 (10.0%)	13.30	0.002 HS
	ID	0	0	6 (31.6%)	7 (36.8%)	6 (31.6%)	0		
Visual-Spatial reasoning	Control	0	0	2 (6.7%)	4 (13.3%)	23 (76.7%)	1 (3.3%)	2.89	0.423 NS
	ID	0	0	1 (5.3%)	6 (31.6%)	12 (63.2%)	0		

Fisher's Exact Chi-Square Test

All items of non- verbal items of Stanford Binet fifth edition were non - significant between control group and ID group except Quantitative Reasoning and Working Memory items were highly significant difference between control group and ID. All cases in both group presented from border line mentality except there were four cases has affection in quantitative reasoning and presented with mild mental retardation.

Table 5: Distribution between degree of total non - verbal IQ and its subitems among control and IDA

	control	Moderate	mild	borderline	Below average	average	High average	X ²	P value
Fluid Reasoning	Control	0	0	1 (16.7%)	6 (50.0%)	13 (68.4%)	10 (83.3%)	21.83	<0.001 HS
	IDA	2 (100%)	9 (100%)	5 (83.3%)	6 (50.0%)	6 (31.6%)	2 (16.7%)		
Knowledge	Control	0	0	0	11 (45.8%)	18 (85.7%)	1 (50.0%)	24.85	<0.001 HS
	IDA	1 (100%)	8 (100%)	4 (100%)	13 (54.2%)	3 (14.3%)	1 (50.0%)		
Quantitative Reasoning	Control	0	0	0	6 (42.9%)	17 (68.0%)	7 (87.5%)	20.42	<0.001 HS
	IDA	3 (100%)	7 (100%)	3 (100%)	8 (57.1%)	8 (32.0%)	1 (12.5%)		
Working Memory	Control	0	0	0	8 (44.4%)	19 (86.4%)	3 (75.0%)	29.70	<0.001 HS
	IDA	2 (100%)	8 (100%)	6 (100%)	10 (55.6%)	3 (13.6%)	1 (25.0%)		
Visual-Spatial reasoning	Control	0	0	2 (25.0%)	4 (33.3%)	23 (74.2%)	1 (50.0%)	18.0-5	<0.001 HS
	IDA	0	7 (100%)	6 (75.0%)	8 (66.7%)	8 (25.8%)	1 (50.0%)		

Fisher's Exact Chi-Square Test

All items of non - verbal items of Stanford Binet fifth edition were highly significant between control group and ID A group. In IDA, there were many cases had mild & moderate mental retardation.

Table 6: Distribution and comparison between degree of total non - verbal IQ and its subitems among IDA and ID

		Moderate	mild	borderline	Below average	average	High average	X ²	P value
Fluid Reasoning	ID	0	0	4 (22.2%)	4 (22.2%)	8 (44.4%)	2 (11.1%)	9.38	0.09 NS
	IDA	2 (6.7%)	9 (30.0%)	5 (16.7%)	6 (20.0%)	6 (20.0%)	2 (6.7%)		
Knowledge	ID	0	0	2 (10.5%)	9 (47.4%)	8 (42.1%)	0	11.79	0.03 S
	IDA	1 (3.3%)	8 (26.7%)	4 (13.3%)	13 (43.3%)	3 (10.0%)	1 (3.3%)		
Quantitative Reasoning	ID	0	4 (21.1%)	1 (5.3%)	5 (26.3%)	9 (47.4%)	0	4.32	0.505 NS
	IDA	3 (10.0%)	7 (23.3%)	3 (10.0%)	8 (26.7%)	8 (26.7%)	1 (3.3%)		
Working Memory	ID	0	0	6 (31.6%)	7 (36.8%)	6 (31.6%)	0	10.59	0.06 NS
	IDA	2 (6.7%)	8 (26.7%)	6 (20.0%)	10 (33.3%)	3 (10.0%)	1 (3.3%)		
Visual-Spatial reasoning	ID	0	0	1 (5.3%)	6 (31.6%)	12 (63.2%)	0	10.73	0.030 S
	IDA	0	7 (23.3%)	6 (20.0%)	8 (26.7%)	8 (26.7%)	1 (3.3%)		

Fisher's Exact Chi-Square Test

All items of non - verbal items of Stanford Binet fifth edition were non - significant between ID and IDA groups except knowledge and VS were significant difference between ID & IDA in affection of cases by mental retardation.

DISCUSSION

Previous studies concluded that ID had negative impacts on cognition, behavior, and motor skills and highlights external factors^[11]. This study discusses the impact of ID & IDA on NV-IQ abilities, which reflects cognitive function.

Development of brain areas such as the hippocampus, myelination of neurons, and function of neurotransmitters were affected by malnutrition^[12]. Iron deficiency with an impaired cognitive performance linked to multiple biological mechanisms, as iron level reduced in the nervous system, even before RBC production is affected^[13]. *Beard 2001* reported that the brain is sensitive to serum iron and its effects on cognition^[14]. The ID affects the myelination rather than the dopamine system across the synapses^[15]. *Beard 2001*, revealed

that the IQ is correlated with the total cerebral volume of cortical grey matter by iron deficiency^[16]. *McLean et al.* described nutritional anemia as the result of iron deficiency^[17].

The data of the current work determined the mean score of each item of the non-verbal abilities of SB-5th among the studied sample. Data showed that fluid reasoning got worst among children with IDA. The task examined the ability to solve problems visually. Non - verbal knowledge examines the function of cognition and the development of pragmatics. *Cummings*, demonstrated that the relationship between cognition and pragmatics is bidirectional^[18]. The pragmatics include cognitive roots^[18].

On the other hand, the mental examination should incorporate utterance explanation and beliefs of fixation. Non-verbal, quantitative reasoning could

solve numerical problems - non-verbally. In agreement with *Cross et al.*, children with developmental language disorder performed significantly lower than their peers on mathematical tasks^[19]. Assessment of visual working memory (WM) included holding visual information in the short-term memory and transforming it. *Leonard et al.* examined memory abilities and found that language scores correlated to processing speed and memory abilities.

In this study, all non-verbal items of Stanford Binet fifth edition were non-significant between the control and ID groups, except Quantitative Reasoning and Working Memory items. The findings agreed with the results of *Handa et al.* revealed that iron deficiency impairs the activities that involve verbal working memory^[21].

Assessment of visuospatial abilities included seeing relationships among figural objects and describing or recognizing spatial orientation. *Tomalski*, reported that human speech is a multisensory experience and the most important modalities for language comprehension and production are visual-spatial modalities^[22].

Cooper, reported that the integrity of the social pragmatics aspects resulted from the adequacy of audiovisual processing of the speech^[23]. This fact could explain the deficit of visuospatial skills among IDA and magnified the role played by the visual information from speakers' mouths. The direction of movement of the articulator in the space and the motherese increase the vocabulary number before the age of one year. *Lewkowicz & Hansen-Tift* reported that toddlers as young as a few months could match speech sounds and lip movement^[24]. *Moradi et al.* suggested that audio-visual training reinforces the route to phonological and lexical representation to facilitate their further access^[25]. The visuospatial skills were presumed by some research work to be responsible for morpheme errors.

Aspuru et al., reported that one of the commonest causes of ID is insufficient dietary iron intake or malabsorption, which is uncommon in developed countries but common in developing areas^[5]. In this study, all the children had faulty eating habits, including consuming fast food often and rarely consuming high biological value proteins, green leaves, and fresh fruits, leading to decreased intake and absorption of iron, resulting in either ID or IDA. This agreed with an Ethiopian study where nutritional iron deficiency anemia was diagnosed in 37.3% of the children^[26].

CONCLUSION

IDA is the most common type of anemia related to malnutrition, IDA prevalence in Egypt is 43%, a recent

common public health problem. The brain is sensitive to iron depletion, which affects cognition and nutritional anemia due to iron deficiency. So, finally, there is necessitating assessing NV-IQ and iron status in any child with delayed language development with poor attention span, intelligence, sensory perception functions, emotions, and behavior, especially with faulty eating habits.

ABBREVIATIONS

CBC: Complete Blood Count

IQ: Intelligent Quotient

IDA: Iron Deficiency Anemia

ID: Iron Deficiency.

MCV: Mean corpuscular volume

MR: Mental retardation

NV-IQ: Non- Verbal -Intelligent Quotient

RBC: Red blood cell

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- Data Sharing Statement: Deidentified individual participant data will not be made available.
- Article summary: There is necessitating of assessing of NV-IQ, and iron status in any child with DLD with poor attention, especially with condition of faulty eating habits.

CONFLICT OF INTEREST

There are no conflicts of interest.

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