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CORRELATION BETWEEN IRON DEFICIENCY ANEMIA AND COGNITIVE FUNCTION IN SCHOOL CHILDREN

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ABSTRACT

Background: Iron deficiency is the most common cause of anemia in the world. It is a major public health concern in preschool children and pregnant women in the developing world. Anemia also reduces physical work capacity and cognitive function and adversely affects learning and scholastic performance in school children entering adolescence.

Aim of work: The aim of this work is to assess the effect of iron deficiency anemia (IDA) on different I.Q parameters as memory, attention, language, and concentration, etc. by using Stanford Benit scale 4 (S B 4)

Patients and methods: This prospective case cohort study was carried out at the outpatient clinic, Al-azhar University Hospital and Sidi-Galal health insurance clinic at Assiut city Egypt from January 2015 to June 2015. The study included 90 children (60 female and 30 male) 60 of them suffering from IDA (40 female and 20 male) in addition to 30 apparently health children of matched age and sex as control group (20 female and 10 male). The studied cases divided into three groups based on their age and degree of anemia as regard to hemoglobin level according to World Health Organization (WHO) 2002) (table 1). All cases were submitted to full history taking, clinical examination, and laboratory investigations. Finally, StanfordBenit (SB) scale was applied before and after treatment.

Results: There was statistically significant decrease of hemoglobin, mean cell volume (MCV), mean cell hemoglobin (MCH), serum iron (SI), and serum ferritin in study group when compared to control group. However, there was significant increase of RDW and total iron binding capacity in patients group when compared to control group. In addition, there was significant decrease of information, arithmetic, digit span, verbal IQ, picture completion, picture arrangement, block design, object assembly and total SB score in patients group when compared to control group. In study group, iron therapy leads to improvement of mental function in the following parameters (digital span, verbal IQ, picture completion, picture arrangement, block design, object assembly and total SB score. Finally, there was proportional (positive), significant correlation between serum ferritin and IQ before and after iron therapy in patient with iron deficiency anemia.

Conclusion: results of the present study revealed that, iron deficiency anemia had harmful effect on mental function as well as laboratory parameters.

Keywords: Stanford Binet; iron deficiency, anemia

INTRODUCTION

Iron deficiency is the most common cause of anemia in the world **(Scott, 2007).** It is a worldwide nutritional problem, affecting all age groups and all socio-economic levels of society **(Leung & Chan, 2001).** It is a common problem in Egypt, with a very high prevalence rate **(El-Sahn, 2000).**It is a major public health concern in preschool children and pregnant women in the developing world. While many studies have examined these two at-risk groups, there is a paucity of data on anemia in school children living in developing countries **(Leenstra et al., 2004).** Iron deficiency anemia (IDA) occurs when the dietary intake or absorption of iron is insufficient, and hemoglobin, which contains iron, cannot be formed **(Brady, 2007).**Even moderate anemia (hemoglobin< 10 g/dL) has been consistently shown to be associated with depressed mental and motor development in children **(Grantham &Ani, 2001).** Anemia also reduces physical work capacity and cognitive function and adversely affects learning and scholastic performance in school children entering adolescence **(Aboussaleh et al., 2004).**

Iron deficiency is an important cause of decreased attention span, alertness and learning ability, so it can worsen scholastic performance **(Ayala et al., 2008).** Iron deficiency anemia in children has been associated with retardation in growth and the

cognitive development **(Bandhu *et al*., 2003).**

Although research on cognitive function in iron deficient children is diverse, it suggests that there may be alterations in attentional process, learning ability, memory and cognitive test performance in children associated with iron deficiency **(Stacky, 2005).**Diagnosis of iron deficiency (ID) is not always easy. Low serum levels of ferritin or transferrin saturation, imply a situation of absolute or functional ID. It is sometimes difficult to differentiate IDA from anemia of chronic diseases **(Brotanek et al., 2007).**

The serum ferritin is the sole useful measure of iron stores, setting the lower limit at 10 µg/dL for some populations in order to increase the sensitivity of the test **(Hopkins et al., 2003).**Diagnosis is supported by low mean corpuscular volume (M.C.V) and increased red cell distribution width (R.D.W) **(Emel, 2005).**

An intelligence quotient, or IQ, is a score derived from one of several standardized tests designed to assess human intelligence **(Stern, 1914).**The Stanford Binet Intelligence Scale , fourth edition (SB4), : All participants (patients and controls) underwent assessment by the Arabic version **(Melika, 1998)**of Stanford–Binet test (fourth edition) astandardized and well validated psychometric testing used to assess memory, attention, language, and concentration. Stanford–Binet test is formed of vocabulary, comprehension, verbal relations test, abstract visual reasoning test, quantitative reasoning test, memory for sentences test, bead memory test and intelligent quotient. This test is characterized by its acceptability to children, and relevance to daily livings activities in children group of population **(Nicolas et al., 2013).** "The Stanford-Binet Intelligence Scale has a long and rich tradition, which began in 1916 when Lewis M.Terman completed his American revision of the 1908 Binet - Simon scale. At that time it was called the Stanford Revision of the Binet - Simon scale. Through various editions in 1937, 1960, and 1986, the Stanford-Binet has become widely known as a standard measure for intellectual abilities **(Delany & Hopkins, 1986).**

Aim of the work

The aim of this work is to assess the effect of iron deficiency anemia (IDA) on different I.Q parameters as memory, attention, language, and concentration, etc. by using S B scale 4.

PATIENTS AND METHODS

This prospective case cohort study was carried out at the outpatient clinic, Alazhar University Hospital and Sidi-Galal

health insurance clinic at Assiutcity from January 2015 to June 2015.The study included 90 children (60 female and 30 male) 60 of them suffering from IDA (40 female and 20 male) in addition to 30 apparently health children of matched age and sex as control group (20 female and 10 male).

The studied cases divided into two group: control group, and patient group which subdivided into subgroups {mild group, moderate group and severe group with iron deficiency anemia (IDA) according (WHO 2002)}.

Table (1): Hemoglobin value by age and sex

Age group	Normal	Mild anemia	Moderate anemia	Severe anemia
6 months - 5 years	12.5	10.0-10.9	7.0-9.9	<7.0
6-11 years girls	13.0	10.5-11.4	7.5-10.4	<7.5
12 -19 years girls	13.5	10.0-11.9	7.0-9.9	<7.0
6-11years boys	13.5	10.5-11.4	7.5-10.4	<7.5
12-14 years boys	14	10.0-11.9	7.0-9.9	<7.0

(WHO, 2002)

Exclusion criteria: children with one or more of the following criteria were excluded from the study: 1) Age below 5 years or older than 14 years; children with anemia other than IDA; children with neuropsychiatric disorders; and medication known to modify cognitive function of the brain.

All children included in this study were submitted to full history taking (especially dietetic, parasitic infestation or history of chronic disease). Then, all children were examined clinically in a detailed and systematic manner. Clinical examination included anthropometric measurements, pulse and blood pressure; and we searched for relevant clinical signs such as pallor, jaundice, pitryasisAlba, pagophagia, irritability, anorexia tachycardia, systolic murmur, other vitamin deficiency, splenomegaly and other symptoms of IDA. Then laboratory investigations to diagnose IDA were done included (Hb%, M.C.V, M.C.H, R.D.W, S.I, T.I.B.C, S.ferritin). Finally, Stanford-Binet Intelligence Scale was applied for all studied children **(Delany& Hopkins, 1986), 4th**edition, modified by **(Melika, 1998).**

All patients received iron therapy in dose of 6 mg/kg elemental iron for three months until complete recovery of iron storage and normal serum ferritin and re-examined again with both laboratory tests and Stnaford-Binet (SB) scale.

Statistical analysis: The results of the current study were analyzed using a statistical package for social science (SPSS) computer package, version 16, running on

International Business Machines (IBM) compatible computer. Categorical data were presented as relative frequency and percent distribution, while numerical data were expressed as mean ± standard deviation. The Chi square test and unpaired samples (t) test were used for comparison between groups in categorical and quantitative data respectively. Correlation between two parameters was calculated using Pearson correlation coefficient (r). p value < 0.05 was considered significant.

RESULTS

In the present study, there was no statistically significant difference between patients and controls as regard to sex or residence distribution. 33.3% of patients group were males. 33.3% of each group was from urban residence. The most common clinical findings in study group were pallor and anorexia (100.0% of cases); then pica in 58.3% of patients, and the least was splenomegaly in 1.6% of cases. On the other hand, there was statistically significant decrease of hemoglobin, mean cell volume (MCV), mean cell hemoglobin (MCH), serum iron (SI), and serum ferritin in study group when compared to control group. However, there was significant increase of RDW and total iron binding capacity in patients group when compared to control group (table 2).

As regard to cognitive function, there was significant decrease of information, arithmetic, digit span, verbal IQ, picture completion, picture arrangement, block design, object assembly and total Stnaford-Binet (BS in patients group when compared to control group (table 3).

In study group, iron therapy leads to statistically significant improvement in hemoglobin, MCV, MCH, serum iron, and serum ferritin; while there was significant decrease in RDW and total iron biding capacity after treatment when compared to corresponding values before treatment. In addition, iron therapy leads to improvement of mental function in the following parameters (digital span, verbal IQ, picture completion, picture arrangement, block design, object assembly and total SB score (table 4).

Comparing subgroups to control group, there was non-significant difference between cases with mild IDA when compared to corresponding control group. On the other hand, there was statistically significant difference in all studied parameters of SB scale between control group from one side and each of subgroups (moderate and sever) from other side. This means that, cases with moderate and severe IDA had significant decrease in all parameters when compared to control group (Table 5).

Table (2): Comparison between cases and controls as regard to demographics, clinical and laboratory findings

		Patients (N=60)	Controls(N=30)	P value
Sex	Male	20 (33.33%)	10 (33.3%)	> 0.05 (NS)
	Female	40 (66.66%)	20 (66.6%)	
Residence	Urban	20 (33.33%)	10 (33.33%)	> 0.05 (NS)
	Rural	40 (66.66%)	20 (66.66%)	
Clinical Findings	Pallor	60 (100.0%)	-	-
	Pica	35 (58.3%)	-	-
	Anorexia	60 (100%)	-	-
	Irritability	30 (50%)	-	-
	Koilonychia	22 (36.6%)	-	-
	Tachycardia	29 (48.3%)	-	-
	Systolic murmur	21 (35%)	-	-
	Splenomegaly	1 (1.6%)	-	-
CBC	H.B (g/dl)	9.15 ± 2	13.5 ± 0.69	<0.001*
	M.C.V (fl)	69.1 ± 4.92	83 ± 4.20	<0.001*
	M.C.H (pg/dl)	22.5 ± 1.70	32 ± 2.18	<0.001*
	R.D.W (%)	17 ± 1.20	13± 1.25	<0.001*
Iron profile	S.I (µg/dl)	27.5 ± 4	85 ± 6	<0.001*
	T.I.B.C (µg/dl)	628.4 ± 50	282.5 ± 38.92	<0.001*
	S.Ferritin (µg/dl)	5.75 ± 2	16.5 ± 3	<0.001*

In the present work, there was proportional (positive), significant correlation between serum ferritin and IQ before and after iron therapy in patient with iron deficiency anemia.

Table (3): Comparison between cases and controls as regard to cognitive function

Variable	Patient (N=60)	Control (N=30)	Sig. (P value)
Information	8.51 ± 2.13	9.14 ± 2.54	<0.05*
Comprehension	8.09 ± 2.97	8.14 ± 2.89	>0.05(NS)
Arithmetic	8.55 ± 4.41	9.86 ± 3.98	<0.01**
Similarities	8.91 ± 3.05	9.07 ± 3.01	>0.05(NS)
Vocabulary	8.01 ± 3.57	8.86 ± 3.45	>0.05(NS)
Digit span	4.95 ± 2.06	6.93 ± 2.06	<0.01**
Verbal I.Q	3.15 ± 2.74	5.93 ± 2.5	<0.001***
Picture completion	7.19 ± 2.43	9.29 ± 2.41	<0.001***
Picture arrangement	7.68 ± 2.01	9.07 ± 2.98	<0.001***
Block design	7.65 ± 2.03	8.71 ± 2.31	<0.05*
Object assembly	7.74 ± 1.98	8.14 ± 2.05	<0.05*
Total	80.43 ± 3.36	93.14 ± 2.74	<0.001***

P value < 0.05 (significant); P value > 0.05 (non-significant); * significant , ** moderate significant , * highly significant**

Table 3 showed that there is a highly statistically significant difference between patients with iron deficiency anemia and control group as regarded to inelegance quotient parameters.

Table (4): Effect of iron therapy on laboratory findings and mental function in study group after three months of therapy

Variable	Patient before iron therapy (N=60)	Patient after iron therapy (N=60)	Sig. (P value)

C.B.C	H.B (g/dl)	9.15 ± 2	13.5 ± 1.5	< 0.001*
	M.C.V (fl)	69.1 ± 4.92	85.5 ± 5	< 0.001*
	M.C.H (pg/dl)	22.5 ± 1.70	31.2 ± 1.8	< 0.001*
	R.D.W (%)	17 ± 1.20	13.5 ± 0.5	< 0.001*
Iron profile	S.I (µg/dl)	27.5 ± 4	65.5 ± 5	< 0.001*
	T.I.B.C (µg/dl)	628.4 ± 50	260.5 ± 20	< 0.001*
	S.Ferrtin (µg/dl)	5.75 ± 2	15.5 ± 2	< 0.001*
Mental function	Information	8.51 ± 2.13	8.97± 2.55	>0.05(NS)
	Comprehension	8.09 ± 2.97	8.12± 2.98	>0.05(NS)
	Arithmetic	8.55 ± 4.41	9.02± 4.14	>0.05(NS)
	Similarities	8.91 ± 3.05	9.03± 3.07	>0.05(NS)
	Vocabulary	8.01 ± 3.57	8.55± 3.56	>0.05(NS)
	Digit span	4.95 ± 2.06	6.65± 2.06	<0.01**
	Verbal I.Q	3.15 ± 2.74	6.24± 1.58	<0.001***
	Picture completion	7.19 ± 2.43	8.84± 1.98	<0.001***
	Picture arrangement	7.68 ± 2.01	8.37± 2.01	<0.001***
	Block design	7.65 ± 2.03	8.02± 1.98	<0.05*
	Object assembly	7.74 ± 1.98	8.1± 2.06	<0.05*
	Total	80.43 ± 3.36	89.93± 2.54	<0.001***

This table 4 showed that there is a highly statistically significant differences of patients with iron deficiency anemia before and after iron therapy as regarded the IQ parameters (digit span – verbal I.Q – picture completion – picture arrangement – block design – object assembly) tested with Stanford benit scale 4.

Table (5): Comparison between patients groups and control group as regard to cognitive function.

	Degree of anemia / Variable	Diseased Group			Control Group	Sig. (P value)		
		Mild (A)	Moderate (B)	Severe (C)		G(A) vs Control	G(B) vsControl	G (C) vs control
	Information	9.14 ± 2.93	8.85 ±2.86	7.8 ± 2.68	9.05 ±2.45	>0.05(NS)	<0.05*	<0.001*
	Comprehension	8.02 ± 3.15	7.95 ±2.89	6.98 ±3.05	8.65 ± 2.98	>0.05(NS)	<0.05*	<0.001*
	Arithmetic	9.06 ± 4.38	8.91 ±3.59	7.09 ±3.21	9.67 ± 3.89	>0.05(NS)	<0.05*	<0.001*
	Similarities	8.95 ± 3.02	8.79 ±2.98	7.06 ±2.68	9.47 ± 3.1	>0.05(NS)	<0.05*	<0.001*
	Vocabulary	8.5 ± 2.72	8.31 ±2.45	7.59 ±2.36	8.95 ± 3.54	>0.05(NS)	<0.05*	<0.001*
	Digit span	6.63 ± 1.07	6.41 ±1.21	4.05 ±1.06	7.89 ± 2.6	>0.05(NS)	<0.05*	<0.001*
	Verbal I.Q	7.03 ± 2.6	6.92 ±2.31	2.05 ±2.62	6.69 ± 2.5	>0.05(NS)	<0.05*	<0.001*
	Picture completion	9.15 ± 2.48	8.98 ±2.02	6.09 ±2.31	9.31 ± 2.14	>0.05(NS)	<0.05*	<0.001*
	Picture arrangement	9.01 ± 2.01	8.95 ±1.89	6.03 ±1.94	8.89 ± 2.89	>0.05(NS)	<0.05*	<0.001*
	Block design	8.69 ± 2.3	8.08 ±2.04	6.7 ± 2.06	8.09 ± 2.31	>0.05(NS)	<0.05*	<0.001*

	Object assembly	**8.04 ± 2.07**	**7.85 ±2.05**	**6.04 ±2.05**	**8.43 ± 2.05**	**>0.05(NS)**	**<0.05***	**<0.001***
	Total	**92.22±2.97**	**90 ± 2.39**	**67.48±2.36**	**95.09 ± 2.76**	**>0.05(NS)**	**<0.05***	**<0.001***

I.Q (intelligence quotient) ' n=number'

Table 5 showed that there is a highly statistically significant differences between patients with severe iron deficiency anemia and controls as regarded to intelligence quotient parameters (digit span – verbal I.Q – picture completion – picture arrangement – block design – object assembly) and also there is a statistically significant differences between patients with moderate iron deficiency anemia and controls and there is no statistically significant differences between patients with mild iron deficiency anemia and controls.

DISCUSSION

Our aim of this prospective study was to evaluate the effect of iron deficiency anemia (IDA) on different IQ parameters as memory, attention, language, and concentration, etc. This study conducted on 90 children (60 of them suffering from IDA in addition to 30 apparently health children of matched age and sex as control group).The groups were recruited from Pediatric outpatient clinic Al-azhar University Hospital and SidiGalal health insurance clinic at Assiut city. Those with IDA classified according to their age into two groups. The first group (group 1) their age from ≥5-<10 yrs. The second group (group 2) their age from ≥10 – 14;and each group will be divided into three sub groups according to HB level in to mild (group A) , moderate (group B) and sever (group C).Also the control was classified according to their age into two groups. The first group (group 3) their age from ≥5-<10 yrs. The second group (group 4) their age from ≥10 -14

Regarding to demographic characteristics (age, sex, residence) of the all studied patients with iron deficiency anemia (IDA) and all controls there are no statistically significant differences were found between patients and controls (P value > 0.05). These results were found to be in agreement with **(Al-Sharbatti et al., 2003).**The high prevalence of iron deficiency among this age group is explained by the increased needs for iron due to rapid growth, low intake of iron-rich foods, inappropriate dietary choices, intestinal parasitic infestation and frequent consumption of tea with meals, all or in various combinations **(Al-Sharbatti et al., 2003).**

Regarding to clinical characteristics of all studied patients with iron deficiency anemia (IDA) (table 2) we found that pallor

and anorexia are the commonest manifestations among IDA patients (100%), followed by Pica (58.3%) irritability (50.00%) then tachycardia (48.3%) and Koilonychia (36.6%) then Systolic murmur (35%) and only (1.6%) with splenomegaly. The previous results regarding to Clinical characteristic were found to be in agreement with **(Petranovic et al., 2008).**

Regarding to intelligence quotient (IQ) parameters among all studied patients with iron deficiency anemia (IDA) before and after iron therapy (table 4) we found that there is a highly statistically significantly differences of verbal I.Q, picture completion and picture arrangement of all patients with iron deficiency anemia before vs after iron therapy (P value <0.001) while there is a moderately statistically significantly differences of digit span of all patients with iron deficiency anemia before vs after iron therapy (P value <0.01) while there is no statistically significantly differences of arithmetic, comprehension, similarities, vocabulary and information of all patients with iron deficiency anemia vs control (P value >0.05) while there is a low statistically significantly differences of block design and object assembly of all patients with iron deficiency anemia before versus after iron therapy (P value <0.05). The previous results regarding to intelligence quotient (IQ) parameters among all studied patients with iron deficiency anemia (IDA) versus control were found to be in agreement with **(Oner et al., 2008).**

In a study of **Anthony (2004)** on 33 iron-deficient, but otherwise normal, he found that children who were given an iron supplement became less hyperactive, and performed better on verbal learning and memory tests. This study suggested that iron deficiency may cause hyperactive behavior and cognitive problems in some children that may be reversible when the deficiency is treated. Iron is a co-enzyme in the anabolism of catecholamines and it is essential for the creation of certain neurotransmitters. It helps to regulate the activity of the neurotransmitter dopamine, which probably accounts for the association of iron deficiency with neurological problems. This is explained by **Beckett et al. (2000)** who reported that observational studies have postulated a positive effect on I.Q due to indirect effects of iron supplementation – improvement in immunity leading to decreased incidence of infections, and improvement in appetite and consequently the intake of energy.

Our result revealed that there is a significantly statistically positive correlation

between level of serum ferritin and total I.Q in all patients with IDA before and after iron therapy. The previous results regarding to correlation between level of serum ferritin and total I.Q in all patient with IDA before and after iron therapy were found to be in agreement with **(Ryan, 2009).** This is explained by the fact that iron plays an important role in many metabolic processes, including oxygen transport, oxidative metabolism, and cellular growth during childhood, and an inadequate supply of iron results in iron-deficiency anemia that is associated with morbidity and impaired I.Q **(Ryan, 2009).**This agrees with the results of a study conducted by **Sungthong and Mo-suwan (2002)** on 427 school children from two schools in southern Thailand. Iron status was determined by hemoglobin and serum ferritin concentrations, and cognitive function in this study was measured by IQ test and school performance. They found that children with iron deficiency anemia consistently had the poorest cognitive function. Also it was found that cognitive functions increased with increased hemoglobin concentration in children with iron deficiency, but did not change with hemoglobin concentration in children with normal serum ferritin level **(Sachdev et al., 2005).**

In short, results of the present study revealed that, iron deficiency anemia had harmful effect on cognitive function as well as laboratory parameters.

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