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Research Article

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Assessment of Serum Ferritin Levels and RBC'S Parameters in Children with Attention-Deficit Hyperactivity Disorder (ADHD) and Learning disabilities (LD)

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Abstract

Objectives: Evaluation of serum Ferritin levels and RBC'S parameters among children with ADHD and LD children, using ferritin levels and RBC'S parameters in order to accept or reject the hypothesis of multifaceted nature of ADHD and LD.

Methodology: A sample of 40 children with ADHD and 40 cases with LD (case group) and 40 control children are subjected to assessment of serum Ferritin and RBC's parameters.

Results: Mean Serum ferritin level among ADHD and LD group were significantly different the mean value among the control group. CBC parameters among ADHD group and LD group (haemoglobin level, RBCs count, MCV and MCH) were significantly different from CBC parameters among the control group.

Conclusions: Serum ferritin and RBC's parameters were significantly lower in ADHD and LD patients compared to non-affected children, Conner test in ADHD was inversely proportional to serum ferritin level so Ferritin as an acute phase reactant gives better picture to iron store in ADHD and LD children so we must Increase screening of iron status and anaemia in ADHD and LD to start iron supplementation as early as possible to reduce symptoms of ADHD and LD patients.

Keywords: Attention-deficit hyperactivity disorder • Ferritin level • Complete blood count • Learning disabilities

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) children represent (5%-15%) of school-aged children, as the comments neuropsychiatric disorder worldwide, in both developing and developed countries [1]. Thapar et al. reported that it could cause other disorders, academic difficulties, and social problems [2]. ADHD children have long-term adverse effects on further social-emotional development, including peers, family members, and teachers [3].

ADHD and Learning Disability is a malfunction in the brain that causes difficulties in comprehension or processing information and causes by different factors [4]. There are types of learning disorders include reading (dyslexia), writing (dysgraphia), and arithmetic (dyscalculia) [5]. Literature among learning disabled showed that dietary allergy to certain food types may result in abnormal metabolic degradation which resulted in production of substances that may affect the vitamins absorption among these group of children. Besides being responsible for abnormal nutritional state it may result in many associated behavioural and academic poor outcome.

Iron is essential for many neurological functioning and development [6]. Iron Deficiency (ID) is the most prevalent nutritional deficiency. Donfrancesco et al. showed that the risk of psychiatric disorders, ADHD, and developmental disorders was increased with ID [7].

Iron plays an essential role as antioxidants, homeostasis of the haemoglobin structure, genetic repair, and Central Nervous System (CNS) function. Ferritin is a stored form of iron that prevents the degrading effects of free iron [8].

Iron has many rules in early brain development, neurotransmitter function, and normal myelination. Deficiency of iron in prenatal or postnatal periods due to either mal-absorption and/or deficiency in dietary intake or subsequent Iron Deficiency (ID) may impair neurodevelopment and long-lasting cause irreversible consequences [9].

So we aimed to evaluate children with ADHD and learning disabilities; using ferritin levels and RBC'S parameters may help understand the multifaceted nature of ADHD and LD.

Materials and Methods

This study was a case-control study conducted on ADHD and LD children who attended paediatrics clinic in Military Production Hospital and Faculty of Postgraduate Childhood Studies, Ain Shams University, for over one year. The study was conducted on 120 subjects and was divided into two groups (case group and control groups). Cases groups consist of (group1: ADHD children, Group2: LD children) written informed consent was obtained from each participant before starting the study. Ethical approval was permitted from the Ethical Committee of Faculty of Postgraduate of Childhood Studies (FPGCS) at Ain Shams University, protocol no. RHDIRB2020110401.

a) Study group included forty ADHD children and forty children with learning disabilities subjected to DSM V criteria, and their age ranged between 5 and 17 years.

b) Control group included 40 healthy children, and their age ranged between 5 and 17 years.

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All the groups were full filled the following:

Inclusion criteria

- All children aged 5-17 years old.
- Diagnosis of ADHD (study group) based on Fifth Edition (DSM-V).
- Normal hearing
- IQ above 70 for ADHD and above 90 in LD children
- Normal motor activity for ADHD.

Exclusion criteria

- Children with epilepsy
- Mental sub-normality, autism, organic brain lesions, psychiatric conditions, haematological disease, acute/chronic medical illnesses, or drug history were excluded during the last three months.

Procedure

Physical examination: Including general examination with vital data assessment and general signs of iron deficiency such as weakness, extreme fatigue, tachycardia, shortness of breath, dizziness, and headache and local examination to exclude other factors affecting child growth and local signs of iron deficiency such as pale skin, cold hands and feet, and brittle nails. Anthropometric measurements including Weight (kg), height (kg) and Body Mass Index (BMI) [weight (kg)/height (m^2)] were calculated.

Laboratory investigations: Including complete blood picture was done for all patients, and Serum ferritin levels were assessed by Enzyme-Linked Immune-Sorbent Assay (ELISA).

Sampling: Six millimetres of venous blood were collected under complete aseptic conditions from patients and controls. They were divided into two vacutainers as follow:

- Two millilitres (2 ml) were collected in a sterile EDTA vacutainer for a complete blood count. These samples were analysed immediately using Coulter Dx instrument for the differential count.
- Four millilitres (4 ml) of blood were collected in a sterile plain vacutainer and were left to clot for 30 minutes, and serum was separated by centrifugation at 3000 rpm for 20 minutes. The separated serum was stored at -20℃. These serum samples were analysed for serum ferritin level using enzyme-linked immune sorbent assay (ELISA); the kit was supplied by a life technologies company (BIOS, Chemux Bioscience,Inc), Hemolyzed samples were discarded.

The ferritin Quantitative test kit is based on a solid phase using enzyme-linked immune sorbent assay (ELISA). The assay system utilized one anti-ferritin antibodies for solid phase (microtiter wells) immobilization and another mouse monoclonal anti ferritin antibody in the antibody enzyme (horseradish peroxidase) conjugated solution. The test sample was allowed to react simultaneously with the antibodies, resulting in the ferritin molecules being sandwiched between the solid phase and enzyme-linked antibodies. After 60 minutes incubation at room temperature, the wells were washed to remove unbound labelled antibodies. A solution of TMP was added and incubated for 20 minutes resulting in the development of a blue color. The color development is stopped with the addition of 2N HCL, and the color was changed to yellow and measured spectrophotometry at 450 nm. The concentration of ferritin was directly proportional to the color intensity of the test sample.

The mean absorbance value for each reference standard set, specimen, controls, and patient samples were all calculated. A standard curve was constructed on graph paper by plotting net absorbance values obtained from each standard on the vertical (y) axis against Ferritin concentrations in ng/mL on the horizontal (x) axis. The absorbance value of each sample was used to determine the corresponding concentration of ferritin in ng\ml from the standard curve.

The specificity of Ferritin kit was determined by measuring interference from high concentrations of human serum proteins (100 ug/dl, transferring; 1000 ug/dl, Ferric chloride, and 12 g/dl of albumin). No significant cross-reactivity was observed.

Statistical methods

All statistical calculations were done using computer programs and SPSS (Statistical Package for the Social Science) version 17. The qualitative data was expressed in the number (N) and personal Chi-square (X^2) test. The quantitative results were expressed as means ± Standard Deviation (SD). An independent t-test was used to compare two groups, e.g. (obese versus normal weight - males versus females). They were finding the relationships between the quantitative variables done by Pearson correlation coefficient. The level of significance was considered at P-value ≤ 0.05.

Results

Descriptive data

Socio-demographic data of the three main groups (Table 1).

Comparative data

Comparison of CBC parameters among the three main groups (Table 2).

Comparison of serum ferritin level between the three main groups (Table 3).

The mean Serum ferritin level of the ADHD group was 15.72 ng/dl while that of the LD group was 25.27 ng/dl, with statistically significant difference between their results and the mean serum ferritin level of the control group (45.4 ng/dl).

Comparison of CBC parameters and serum ferritin level between the three types of ADHD (Table 4).

A mixed type of ADHD (type 3) showed the lowest serum ferritin level and CBC parameters. In contrast, inattentive type (type 2) showed better serum ferritin level and CBC parameters. Lastly, hyperactive type (type 1) showed the best and highest serum ferritin and CBC parameters scores.

Correlative data

Correlation between haemoglobin and ferritin levels in the three groups (Table 5) (Figure 1).

Regarding the ADHD group, serum ferritin level was directly proportionate to haemoglobin level, with a statistically significant difference between scores of both parameters. In the LD group, serum ferritin level was directly proportional to haemoglobin level, with no statistically significant difference between scores of both parameters.

Table 1. Socio-demographic data of the three main groups.

	Sex		Range of age in years (Mean)	P-value
	Males No. (%)	Females No. (%)		
Control	20 (50%)	20 (50%)	5-17 (8.7 years)	0.06 (NS)
LD	18 (45%)	22 (55%)	5-17 (8 years)	0.34 (NS)
ADHD	24 (60%)	16 (40%)	5-17 (8.15 years)	0.55 (NS)

Note: Chi-square test.

Table 2. Comparison of CBC parameters between control and ADHD groups.

	Control	ADHD	P-value		LD	P-value	
	Mean(SD)	Mean(SD)			M (SD)		
Hemoglobin	13.99(0.63)	10.95(0.99)	<0.001*	HS	11.31(0.61)	0.006*	S
Hematocrit	32.00(1.59)	30.03(2.04)	<0.001*	HS	31.70(0.74)	0.002*	S
RBCs	3.37 (0.24)	3.27(0.23)	<0.001*	HS	3.31 (0.07)	<0.001*	HS
MCV	46.70(12.83)	43.55(11.12)	0.012*	S	39.16(7.77)	0.007*	S
MCH	26.57 (5.18)	24.43 (3.31)	0.043*	S	29.78(6.70)	0.003*	S
MCHC	27.27 (3.31)	23.65 (2.23)	0.012*	S	31.51(9.04)	<0.001*	HS
RDW	15.28 (1.63)	13.37 (1.53)	0.003*	HS	12.97(0.64)	<0.001*	HS

Note: Unpaired t-test P value ≥ 0.05 (non-significant), and *p-value<0.05(significant).

Table 3. Comparison of ferritin level between control and ADHD groups.

Serum ferritin	ADHD	Control	P-value	LD	Control	P-value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
	15.72 (7.47)	45.43 (22.06)	<0.001* HS	25.27 (9.23)	45.43 (22.06)	<0.001* HS

Note: Mann Whitney test; *p-value<0.05 (Significant).

Table 4. Comparison of ferritin level between the three types of ADHD.

	Type 1	Type2	Type3
	Mean (SD)	Mean (SD)	Mean (SD)
Serum ferritin	16.93 (8.25)	15.55 (4.77)	14.44 (7.84)
Haemoglobin	11.01 (0.99)	10.70 (0.16)	10.45 (0.95)
Hematocrit	31.03 (0.99)	29.05 (0.99)	29.00 (0.75)
RBCs	3.35 (0.65)	3.37 (0.87)	3.21 (0.63)
MCV	43.55 (.54)	45.75 (0.77)	43.45 (1.18)
MCH	24.70 (3.44)	24.50 (5.05)	24.33 (3.71)
MCHC	24.65 (2.23)	24.00 (3.05)	22.23 (4.10)
RDW	13.80 (0.70)	13.30 (4.00)	12.70 (3.90)

Note: ANOVA except for serum ferritin non-parametric Kruskal-Wallis.

Table 5. Correlation between haemoglobin and ferritin levels in control and ADHD groups.

	Haemoglobin	Ferritin	P-Value
	Mean (SD)	Mean (SD)	
Control	13.99 (0.63)	45.43 (22.06)	<0.001* HS
ADHD	10.95 (0.99)	15.72 (7.47)	
Control	13.99 (0.63)	45.43 (22.06)	0.398 NS
LD	11.51 (0.61)	25.27 (9.23)	

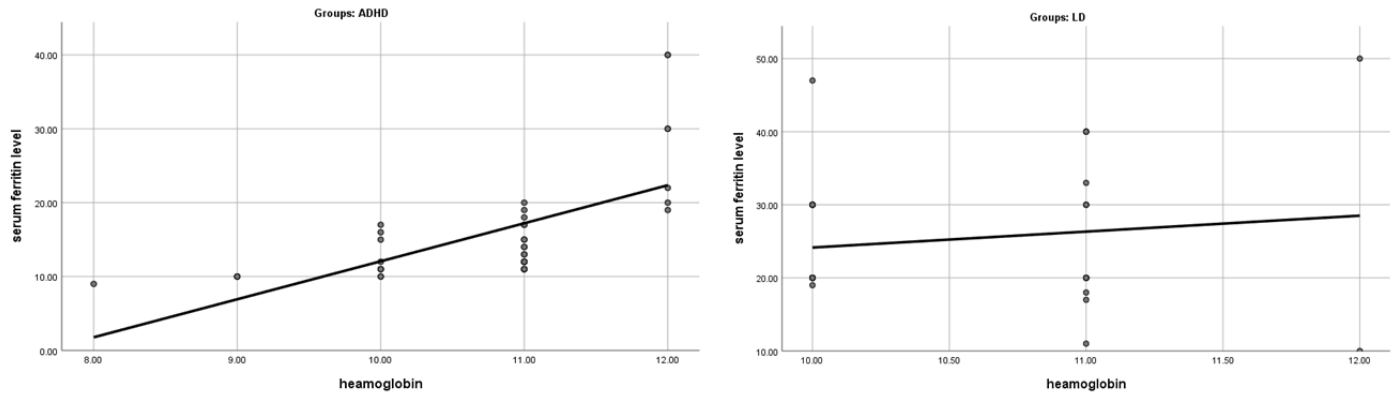

Figure 1. Correlation between haemoglobin and ferritin levels in control and ADHD groups.

Table 6. Correlation between IQ score and serum ferritin levels in control and ADHD groups.

	IQ Score	Ferritin level	P-Value
	Mean (SD)	Mean (SD)	
Control	106.12 (13.42)	45.43 (22.06)	<0.001* HS
ADHD	73.58 (3.75)	15.72 (7.47)	
Control	106.12 (13.42)	45.43 (22.06)	0.016 S
LD	91.62 (11.55)	25.27 (9.23)	

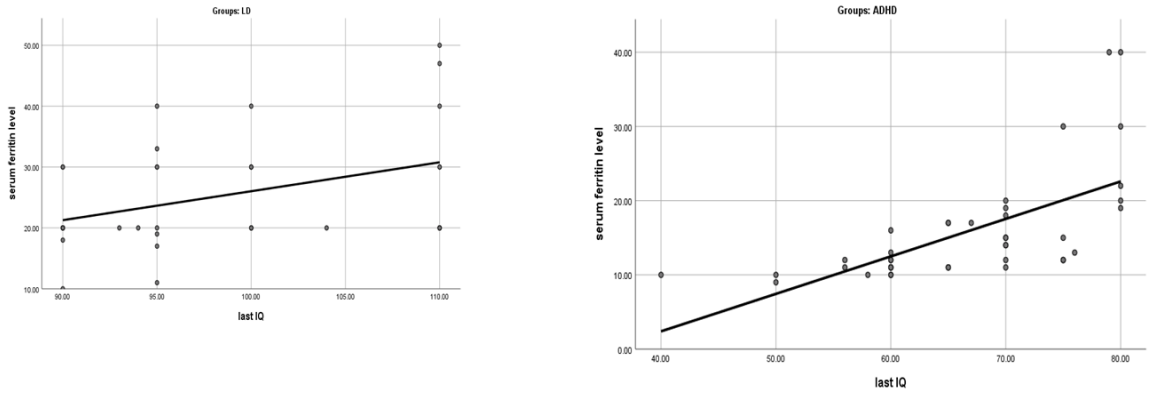

Figure 2. Correlation between IQ score and serum ferritin levels in control and ADHD groups.

Correlation between IQ score and serum ferritin level in the three main groups (Table 6) (Figure 2).

Regarding the ADHD group, serum ferritin level was directly proportionate to IQ scores, with a statistically significant difference between scores of both parameters. In the LD group, serum ferritin level was directly proportional to IQ scores with no statistically significant difference between scores of both parameters.

Discussion

The main aim of this study was to evaluate the ADHD and to learn disabilities children; using ferritin levels and RBC'S parameters may help in understanding the multifaceted nature of ADHD and LD to achieve such goal. The control group in the study was selected to be age and gender-matched with the study groups. Our results showed no significant difference between both groups according to age and gender, so accordingly, both groups are matched, and the age and gender had no effect on the scores. ADHD and LD have different identities, but they may have some similarities in inattention and distraction. So, in this study, we try to find a link or hypothesis for them.

Kessler et al. mentioned that according to the DSM IV, ADHD children represent the symptoms before the age of seven [10]. Therefore, the current work approximates the worldwide age of presentation of ADHD, which means age was eight years old. The diagnosis of LD requires persistent difficulties in one of the following or more: reading, writing, arithmetic, or mathematical reasoning skills during formal years of schooling (American Psychiatric Association) and that age were concurrent with the results of this study (Table 1) [11].

Although the gender was non-significant results statistically in ADHD and LD, these results were in concordance with Bellgrove et al. found that boys and girls are equally likely to have learning disabilities and ADHD [12]. In disagreement with the Hawke et al. found that boys were two times affected than girls with ADHD [13].

In the current work, there was no statistical difference between males and girls with regards to LD. This was in agreement with Hicks et al. found no gender gap between boys and girls regarding learning problems [14]. These results were against Lagae et al. found that boys are more likely to be diagnosed with learning disabilities than girls (12.9% compared to 5.6%) [15]. The girl and the boy ratio varied by countries, ranging from 1:3 to 1:16. This proves that gender has no rule in L D manifestation or severity.

In the present study, group I: ADHD children and group 2: LD children were statistically significantly lower RBCs parameters than the control group (Table 2). These results were in concordance with Sungthong et al. found a correlation between the level of haemoglobin and LD; it was done on 192 LD children, their age ranged from 8 to 12 years old, they found that anaemia was present in 92 students (Hb from 10.0 g/dL to 11.5 g/dL) and the other 100 students (Hb from 14.0 g/dL to 14.9 g/dL) [16].

In the present study, the forty ADHD children had statistically significantly lower serum ferritin levels with a mean of 15.72 ng/dl than the control group with 30.43 ng/dl. Also, as regards the forty LD children had statistically significantly lower serum ferritin levels with a mean of 25.27 ng/dl when compared to control (The serum ferritin<20 ng/dl is considered low) (Table 3).

These results, concordance with Pivina L et al. found that depletion in serum ferritin in children with cognitive and learning problems [17]. Also, Soewondo S et al. found that the children with iron-deficiency anaemia performed significantly poorer in the achievement tests than those children who are non-anaemic [18].

Donfrancesco, et al. found that ADHD children had low magnesium, zinc, copper, and iron levels. Furthermore, iron is essential in dopaminergic regulation. ADHD is accompanied by dopamine releasers (amphetamine, psych stimulants and methylphenidate) [7]. Karama S.et al. found a lack of dopamine, epinephrine, or norepinephrine in these areas of the brain is partly responsible for the symptoms experienced with ADHD patients [19].

Cortese et al., found in his study serum ferritin level in the ADHD group had statistically significantly lower serum ferritin level with a mean of 15.72 ng/dl compared to the control group with a mean of 30.43 ng/dl 6. This study found that type 3 mixed type of ADHD was the lowest serum ferritin level with a mean 14.44 (Table 4). In concordance with Calarge et al. who found that serum ferritin levels were inversely correlated with ADHD children with the lowest ferritin level the most hyperactive, impulsive, and inattentive [20].

Additionally, Sungthong et al. noted no association between serum ferritin and severity or frequency of ADHD in American ADHD participants aged between 5 and 16 years of age [16].

The relationship between ID and ADHD may be explained that ADHD could lead to academic difficulties and social problems; ADHD children have issues associated with deficits in language development and attention. There are several pathophysiological mechanisms, but the main cause is still vague. Low peripheral iron levels may dysregulate dopaminergic neurons, which results in multiple frontal dysfunctions in ADHD [21]. In addition to the dopamine theory, the low ferritin level has an indirect rule in elevated oxidative stress, which is reported in ADHD children. This increased oxidative stress disturbs neurodevelopmental and gene functions and predisposing to the onset of ADHD [22].

Conclusion

Serum ferritin and RBC's parameters were significantly lower in ADHD and LD patients compared to non-affected children, so early treatment with iron supplementation is essential to reduce both symptoms of ADHD and LD patients. We hypothesized that lower iron status and RBCs parameter would accompany lower academic performance and behaviour problems also the most frequent local sign of iron deficiency in both ADHD and LD is pale of skin.

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Disclosure

The authors declare no conflict of interest.

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