Role of Iron in Improving Attention Deficit Hyperactivity Disorder in Children and Adolescents

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Abstract

Background: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting children and adolescents with dangerous psychiatric sequalae if it has not been managed well for long time by medical and psychological therapy.

Objectives: this prospective study is to evaluate the effect of iron in improving ADHD through measuring many parameters which are laboratory and scales before and after iron therapy for almost 3 months and in compared with healthy controls.

Patients and Methods: there are 100 children and adolescents diagnosed clinically as ADHD and assessed for its severity by Conners rating scale, in addition they are associated with iron deficiency anemia. The demographic data, clinical, and laboratory measurements were also collected.

Results: There was a significant difference in both IQ and Conners rating scale values between case and control group, denoting the role of iron in attention, cognition and intelligence.

Also, there was a significant difference between the parameters (HB, serum iron, IBC, ferritin, conners rating scales values, IQ) which were measured for cases members before and after introducing of iron supplement for almost 3 months, as these parameters were improved after introducing iron supplementation.

Conclusion: screening of cases with ADHD for possibility of iron deficiency anemia is considered so important as iron supplementation could be sufficient to avoid bad side effects of other medication for ADHD.

Keywords: ADHD; Iron; IQ; Anemia; Ferritin; Conners' rating scale;Iiron binding capacity (IBC).

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Introduction

According to the estimation of the WHO, iron deficiency is the most common deficiency among children and adolescents. It could be detected sometimes in asymptomatic individuals insidiously and generally manifested by common manifestations such shortness of breath and pallor, as it is having an important role in formation of several metalloproteins such as hemoglobin (Hb), myoglobin, and many enzymes that have a role in cellular metabolism **(Aptekmann et al., 2022).**

Concentration of different neurotransmitters such as dopamine, serotonin, and norepinephrine in different areas of the brain, are affected by the iron deficiency either intracellular or extracellular **(Kim and Wessling-Resnick, 2014).**

Attention-deficit/hyperactivity disorder (ADHD) is stressed lack of control and wildly disruptive behavior that characterized by presence of a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with normal daily functioning or development **(Sonuga-Barke et al., 2010).**

The pathogenesis of ADHD by using tensor imaging suggests alterations in white matter integrity in a range of key fiber pathways which mean affected cognitive functions in cases of ADHD **(Van Ewijk et al., 2012).**

Iron is playing a role in being a cofactor in tyrosine hydroxylase enzyme formation, which is considered so important in formation of neurotransmitters, including serotonin, dopamine, and norepinephrine, also iron deficiency anemia is usually associated with socio-emotional cognitive impairment and educational damages, so that Children with iron deficiency whether manifested by anemia or not are involved in many cognitive problems including decreased intelligence quotient (IQ) and attention problems **(Ferreira et al., 2019).**

We aimed in the current study to assess the correlation between IQ and Conners rating scale in cases with iron deficiency anemia parameters (Hb, TIBC, Ferritin) before and after 3 months of iron supplementation

Patients and Methods

This prospective study was established in the clinics of neuropsychiatric diseases of children and adolescents in Luxor and Minia health insurance and university hospitals. It included 2 groups (case and control) and every one contained 100 members as children and adolescents aging between (7 – 14) years.

The study started in January 2024 and lasted for 4 months, which can be sufficient for iron stores repletion in body by iron supplement **(Granero et al., 2021)**.

Ethical consideration: Minia University, Faculty of Medicine, Institutional Review Board (MUFMIRB), Minia, Egypt, has given its approval to this research, and the ethical code (approval number) is: 1052/02/2024.

Our criteria for choosing the case patients have included the following points:

A. (1) **Case group**: has ADHD patients which diagnosed clinically and assessed by Conners rating scale **(Conners,1981)** according to the Diagnostic and Statistical Manual of Mental Disorders (5th edition) **DMS 5 (Gulati et al., 2020)**, in addition the patients are associated with iron deficiency anemia diagnosed clinically and laboratory.

   Criteria of iron deficiency anemia is: physical manifestations that depend on the severity of anemia, including generic symptoms as fatigue, lassitude, pallor, and generalized lack of energy, also Laboratory investigations including low HB with

low mean corpuscular volume (MCV), serum iron, ferritin, high TIBC **(Clark,2008).**

(2) **Control group**: chosen from outpatient clinics in our university and health insurance hospitals, with no iron deficiency anemia that confirmed clinically and laboratory, also without ADHD manifestations.

B. The rate of conners rating scale values was either mild, moderate, severe which not needed for medical intervention as in profound stages, which were–excluded because they needed medical intervention.

C. The selective cases which were suspected as having iron deficiency anemia due to presence of either fatigue, lassitude, pallor, and generalized lack of energy, were applied for the following investigations to approve iron deficiency anemia:

1. CBC: showing microcytic hypochromic anemia according to the red blood cell indices which show low mean corpuscular volume (MCV) and low mean corpuscular hemoglobin (MCH).
2. serum iron: if it is low, it would be a diagnostic criterion.
3. ferritin: if it is low, it would be a diagnostic criterion.
4. total iron binding capacity (TIBC): if it is high, it would be a diagnostic criterion.
5. Intelligence Quotient (IQ): measured by using Stanford Binet scale edition 5 for all the cases, before and after iron supplement for almost 3 months, in the dose of 3-6mg/kg/day which given orally.

Exclusion criteria

1. All chronic debilitating diseases as chronic kidney diseases, chronic liver diseases, endocrinal diseases and malnutrition disorders.
2. Malignancies such as leukemia, lymphoma, and others.
3. Malabsorption disorders and helminths infestations.
4. Other metabolic and hematological diseases such as aplastic anemia, bone marrow fibrosis or replacement.

Statistical analysis

Data entry and analysis were done using the software program SPSS version 22. We used The Kolmogorov-Smirnov (K-S) test to determine whether a sample follows a specified distribution. Quantitative data presented as mean and SD Qualitative data as frequency distribution independent sample t-test and paired t-test were used for comparison Pearson's Correlation test was used, a P-value of less than 0.05 used as the cutoff for significance.

Results

The study included 100 patients that participated in our research, including 79 males (79%) and 21 females (21%), aged between (7 -14) years, there was 82 patients were with type 3 ADHD and 18 patients were with type 2 ADHD, as shown in (**Table .1)**.

Regarding to the measured (IQ) there was a high statistically significant difference between cases and controls groups as IQ mean value was (69.5 %) before introducing iron supplementation and after that was improved with mean value of (87.5 %) and p value was high significant ($p < 0.001$) as in (**Table .2)**, showing the effect of iron deficiency on the cognition.

Table 1. Personal data and ADHD types of the studied cases

Data	Cases
Age: • **Range** • **mean**	 7-14 9.3±2.02
Sex: • **Male. No, (%)** • **Female. No, (%)**	 79(79%) 21(21%)
Type of ADHD: • **Combined type 3. No, (%)** • **Inattentive type 2. No, (%)**	 82(82%) 18(18%)

Table 2. IQ in the studied groups

IQ	Cases	Controls	p-value
Range	67-72	84-90	0.001*
Mean ± SD	69.5±1.5	87.5±1.5	

*: significant; sample t-test.

Regarding ADHD, Conners rating scale values in case group were high and low in control group with a statistically significant difference between both groups as p value was high significant ($p < 0.001$) as in (**Table.3**). The HB values were significantly low in cases group before iron supplementation and improved after iron supplementation ($p < 0.001$), (**Table .4)**.

Table 3. Conners rating scale in the studied groups

Conners rating scale	Cases	Controls	p-value
Range	58-70	38-42	0.001*
Mean ± SD	64.9±3.5	40.5±1.1	

*: significant; sample t-test.

Table 4. Hemoglobin in the studied groups

Hb	Cases	Controls	p-value
Range	7.6-10.2	11.8-14.2	0.001*
Mean ± SD	8.5 ±0.7	13.1±0.7	

*: significant; sample t-test.

There was a statistically significant difference between all the measured parameters (HB, ferritin, TIBC, serum iron, IQ, and Conners rating scale) for the case group, as their values were low before iron supplementation and improved after iron supplementation, with a high significant p value ($p < 0.001$) as shown in (**Table .5).**

Table 5. Comparison of the studded markers pre- and post-treatment among the studied cases

Data	Pre-treatment	After treatment	p-value
Hb (mg/dl)	8.5 ±0.7	10.6 ± 0.6	0.001*
Ferritin (µ/L)	5.7 ±0.3	18.1 ± 3.1	0.001*

TIBC (micromole/L)	472.7 ±11.9	341.5 ±16.8	0.001*
Serum iron (mcg/dl)	27 mcg/dl ±2.2	101 mcg/dl ±6.9	0.001*
IQ (%)	69.5 % ±1.5	80.5 % ±1.6	0.001*
Conners rating scale	64.9 % ±3.5	54.7 % ±3.7	0.001*

*: significant; paired T test; HB: Hemoglobin; TIBC: total iron binding capacity; IQ: Intelligence Quotient.

There was a negative significant correlation between both Conners rating scale scores and IQ results for the cases before their treatment with iron during 3 months and negative fair correlation after treatment with iron, as shown (**Table .6), (Figs.1.a &1.b)**.

Table 6.Correlation between Conners rating scale before treatment and IQ, Hb, and serum iron

Parameters	correlation coefficient r	P-value
IQ	-0.82	(0.0001*)
Hemoglobin	-0.82	(0.0001*)
Serum iron	-0.49	(0.07)

*: significant; HB: Hemoglobin; IQ: Intelligence Quotient

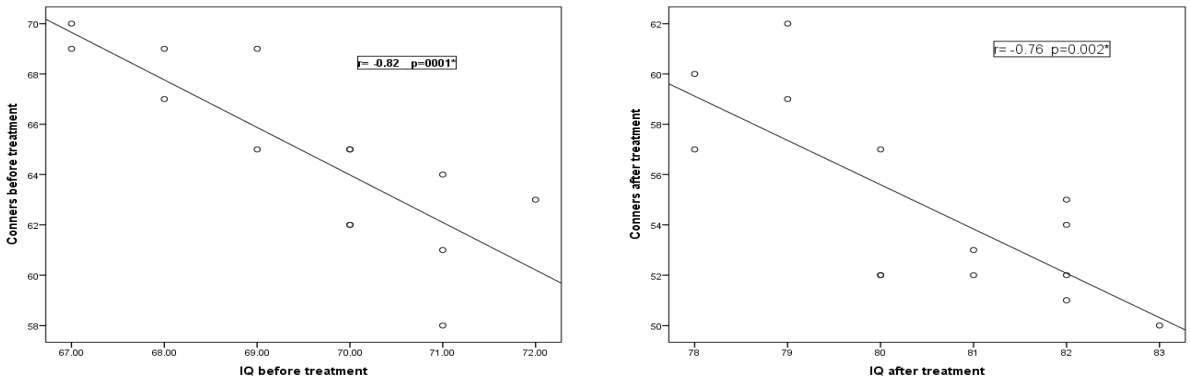

Fig. 1. Correlation between IQ and Conner's rating scale score (a) before treatment (b) after treatment

There is a negative significant correlation between both HB value and conners rating scale values in both before and after iron treatment also there is negative fair correlation between both serum iron and Conners scale values before and after treatment with iron shown in (**Table.7), (Figs 2.a&2.b)**.

Table 7. Correlation between Conners rating scale after treatment and IQ, Hb, and serum iron

Parameters	correlation coefficient r	P-value
IQ	-0.76	(0.002*)
Serum iron before	-0.49(0.07)	(0.07)
HB after	-0.76	(0.0001*)
Serum iron after	-0.39(0.1)	(0.1)

*: significant; HB: Hemoglobin; IQ: Intelligence Quotient.

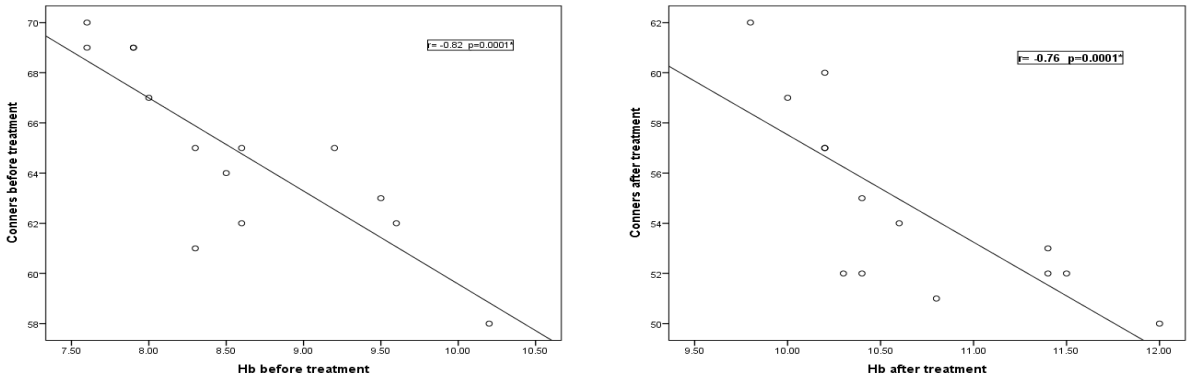

Fig. 2. Correlation between Hb and Conner's rating scale score (a) before treatment (b) after treatment

Discussion

ADHD is considered a disruptive neurobehavioral disorder that characterized by presence of a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with normal development (**Aptekmann et al., 2022**).

Manifestations of inattention can include mind wandering a task, lack of persistence, and disorganization as one of the commonest childhood psychiatric disorders, attention-deficit/hyperactivity ADHD associated with other psychiatric comorbidities, such as disruptive behaviors, antisocial activities, and poor verbal working memory disorders, resulting in impaired learning and social ability (**Biederman et al., 2010**).

However, the specific underlying etiology of ADHD remains unclear and could be suggested that some nutrients deficiency is a precipitating factor. Iron deficiency is one of these nutritional causes, as iron plays an important role in the regulation of dopaminergic activity, and this could potentially be the pathogenesis of ADHD (**Rucklidge et al., 2009**).

This study compared the effect of iron on improvement of cognitive functions and attention in cases of ADHD before and after iron intake.

It showed that iron deficiency with anemia is associated and positively correlated with high values of Conners rating scale scores, these values were more significant in case group, when compared with control group. Also, this study revealed that iron deficiency with anemia is almost affecting cognition that measured for them by Stanford Binet scale edition 5.

Our study revealed lower levels of serum ferritin in children with ADHD before applying iron therapy to them, and by evaluating the efficacy of iron supplementation for anemic children with ADHD, they showed some improvement of symptoms of ADHD, especially the cognitive ones, and that matched with **Villagomez and Ramtekkar (2014),** as they confirmed that ferritin is increased after iron supplementation associated with improvement in cognitive abilities of ADHD.

The importance of iron might be due to its role in myelination of nervous system, which is effective in improvement of memory and learning abilities, and that has been approved by **Daley et al. (2014),** who has approved that iron deficiency leads to poor myelination of nervous system and monoamine metabolism disruption affecting all of memory, learning abilities, motor, psychological and mental disorders.

Tohidi et al. (2021) reported that iron therapy during 30 days improves the severity of ADHD, which we have noticed in our study concerned the anemic children with iron deficiency and their attention

improvement before and after iron supplementation.

Our chosen time for follow up of cases before and after iron therapy was considered enough and acceptable to can show any changes in ADHD cognitive manifestations during iron supplementation **,** and that was matched with **Granero et al. (2021**), who have implanted that ADHD symptoms including attention deficiency-hyperactivity have been improved after 12 weeks of iron supplementation that helped the efficacy of stimulants when combined with, as it is related to the role of iron in adenosine neurotransmission which provided a pathogenic link with glutamate mechanism.

Parisi et al. (2012) suggested that iron deficiency is an important etiopathophysiological factor underlying ADHD and it contributes to ADHD symptoms severity as his suggestion is based on serum ferritin measures as a marker of peripheral iron status, and that reflects deficiency of brain iron in individuals with ADHD.

Cortese et al. (2012) concluded that children with ADHD had significantly lower levels of serum ferritin than healthy ones in their blood samples and with Low iron in the thalamus that is supported by magnetic resonance imaging (MRI) in the putamen, pallidum, caudate, and thalamus.

In contrast to our study, **Calarge et al. (2010**) and **Cortes et al. (2012**) did not find any significant association between serum ferritin levels and response to psychostimulant treatment and failed to find a correlation between serum iron and ADHD, which could be due to the fact that serum iron is affected by many factors that were not considered in the included studies, and it is better if a larger sample sizes, assessed by using the same assay techniques and multiple indices of iron status to provide more conclusive results.

Limitations of our study were the relatively small sample size, not giving the better prediction of iron supplementation effect on improvement of ADHD manifestations because we applied our study only in tow cities including their university and health care hospitals, and was better if that study was applied in many cities in Egypt, so we could be able to generalize our data.

Conclusion

Our study supported the screening for iron deficiency anemia in cases of ADHD, as iron plays an important role in improvement of the cognition and attention disorders plus it could increase the efficacy of some medications of ADHD.in most cases of ADHD that associated with iron deficiency anemia and not of profound levels could be treated enough only by iron supplementation which let them avoid lot of bad side effect that might be happened with other medications.

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