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Effects of Iron Supplementation on Attention Deficit Hyperactivity Disorder in Children Treated with Methylphenidate

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Objective: To evaluate the effect of iron on the attention deficit hyperactivity disorder, treated with methylphenidate.
Methods: This double-blind, randomized placebo-controlled clinical trial was performed on 50 children with attention deficit hyperactivity disorder under the treatment of methylphenidate, with ferritin levels below 30 ng/ml and absence of anemia. They were randomly assigned into two groups of ferrous sulfate and placebo, for 12 weeks. Conners' Parent Rating Scale (CPRS) was used to assess the outcome in the first, sixth, and twelfth weeks.
Results: Almost all CPRS subscales improved in the ferrous sulfate group from the baseline to the endpoint, although only the changes in conduct subscale scores were significant (p = 0.003). There was no significant difference in score changes between two groups in intergroup comparison. Also, the score of learning problems (p = 0.007) in the first six weeks, and conduct (p = 0.023) and psychosomatic (p = 0.018) subscales in the second six weeks were improved in the ferrous sulfate group compared with the placebo group.
Conclusion: Our study showed promising effects of iron supplementation in the improvement of subscales of the CPRS.

KEY WORDS: Attention deficit disorder with hyperactivity; Iron; Child; Methylphenidate.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurobiological syndrome defined as a persistent pattern of inattention/hyperactivity and impulsive behaviors [1,2] which affects 4 to 12% of school-aged children [3], and can lead to anxiety and depression during adulthood, if left untreated [4]. The prevalence rate of this disorder is higher in children than adults, it affects males more than females, however this ratio seems to be balanced in adulthood [5,6]. Moreover, the highest prevalence of ADHD has been reported in South America, Africa, and Oceania [7].

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Children with ADHD may experience major functional impairments such as academic failure, weakness in communication with family members, antisocial behaviors, and lack of self-esteem [8]. ADHD has also been associated with high activity in cradles, lack of sleep, and abundant crying in infancy. The most common characteristics of ADHD are attention deficit, hyperactivity, self-perceived motor incompetence, emotional instability, distraction, impulsivity, memory, thinking, learning disabilities, aggressive behavior, and disobedience [9,10].

The pathophysiology of ADHD is very complicated and its etiology is not well understood. Recent findings support multifactorial hypotheses; it is thought that the cause of ADHD, like other neuropsychological disorders, is a combination of genetics and environmental factors [11-16].

ADHD is usually treated with medication and its first and the most commonly used treatment is methylphenidate; however, various studies have reported that psychiatric intervention is also required [1,17-23]. Clinical

and laboratory studies have shown the potential role of iron deficiency in the pathophysiology of ADHD. Iron deficiency is generally associated with attention and behavioral problems [24]. Prospective studies in children with iron deficiency anemia have shown socio-emotional and educational damages. Children with iron deficiency (with or without anemia) are involved in many cognitive problems including decreased IQ, motor, spatial memory, and selective attention problems, which can last for years [25,26]. Low iron concentration is associated with changes in myelin structure, followed by changes in cortical fibers function, and dopaminergic system. Iron is a tyrosine hydroxylase coenzyme that is involved in the synthesis of dopamine and is related to amino-oxidase activity, which is a dopamine reducer [27,28]. Dopamine is known as a key element in the pathogenesis of ADHD. Therefore, iron storage in the brain may be effective on dopamine-dependent functions and ADHD symptoms [29,30].

Even though serum ferritin levels are associated with ADHD susceptibility [31], the use of iron as complementary medicine in improving symptoms of this disorder needs further investigation, especially despite contradictory results. The present study evaluated the effects of iron supplementation (ferrous sulfate) on the symptoms of children with ADHD, treated with methylphenidate.

METHODS

Patients

This is a randomized double-blind clinical trial with placebo-control; Fifty-four patients assessed for eligibility, 3 of them excluded (do not fulfill inclusion criteria) and one did not follow the protocol, finally it was performed on 50 children with ADHD, aged 5 to 15 years old, who were referred to the child psychiatric clinic of Rasht Shafa Hospital.

All participants were enrolled by a child and adolescent expert psychiatrist and under the treatment of methylphenidate, with associated ferritin levels below 30 ng/ml and absence of anemia (defined as hemoglobin levels less than 11 g/dl). ADHD was diagnosed by diagnostic interview of the corresponding psychiatrist and based on the clinical criteria of Diagnostic and Statistical Manual of Mental Disorders 4th edition, text revision (DSM-IV-TR) [32]. It is necessary to mention that all patients were under the treatment of short-acting form of methylphenidate (Ritalin-by Novartis Pharmaceuticals Corporation) and methylphenidate was matched in both groups in terms of dosage and duration, before entering the study. The treatment in almost all patients were started as soon as they were diagnosed and the dose of methylphenidate had started with 0.3 mg/kg/dose and titrated to the optimal dose that was 20 mg/day in most cases in the time of the study.

Children with mental disorders along with ADHD, severe chronic medical conditions (i.e., malnutrition), mental retardation and other psychiatric comorbidities (such as anxiety; by diagnostic interview of an expert psychiatrist and according to DSM-IV), inflammation or infection, taking medications other than methylphenidate including catecholamines, use of iron supplementation over the past three months, having contraindication of iron supplementation, severe fever (due to the false increase in the level of ferritin), and hypothyroidism were excluded from the study.

The whole study process was under the Helsinki Declaration with parental informed consent for participation in the study was obtained from them. Ethic Committee of Guilan University of Medical Sciences approved this study (no. IRCT201212012269N2).

Procedure

Baseline characteristics such as sex, age, height, duration of disease, family history, and other comorbidities of all subjects were recorded in a prepared proforma.

Patients were randomly assigned into two groups (Random Allocation Blocks). The first group received iron supplementation (ferrous sulfate 300 mg capsule containing 80 mg of elemental iron) and the second group received placebo, for 12 weeks. All subjects took a capsule daily in the morning. Placebos were designed by an expert pharmacologist as starch-containing capsules with exactly similar face to ferrous sulfate. Furthermore, both psychiatrists and patients' parents were uninformed of which ferrous sulfate or placebo patients were taking.

Iron status and patients' laboratory data, including Complete Blood Count, ferritin, serum iron, and Total Iron Binding Capacity (TIBC) were measured at the beginning of the study and at the 12th week.

All patients' parents were asked to fulfill the Conners' Parent Rating Scale (CPRS) questionnaire in the first, sixth,

and twelfth weeks after medication to assess the possible early changes of CPRS scores and final outcome. In addition to the mentioned visits, patients were regularly visited every two weeks all over the study, for possible side effects of the drugs, checking vital signs and assessing the compliance of treatment.

Instrument

To assess the outcome, CPRS questionnaire [33] was applied for all subjects, a 48-items questionnaire that employed a 4-point Likert scale. Higher score in this measure indicate higher severity of the disease. This questionnaire provides a qualitative and quantitative assessment of attention deficit hyperactivity symptoms on five different subscales including conduct problems, learning problems, psychosomatic, impulsive-hyperactive, and anxiety. It also contains Hyperactivity Index (HI) which is more sensitive to demonstrate the treatment effect. It was completed by parents in the first, sixth, and twelfth weeks.

Statistical Analysis

The distribution of quantitative variables was estimated using the Shapiro–Wilks test. To compare the quantitative variables between the groups, independent *t* test, and Paired test were used for the data with normal distribution and Mann–Whitney and Wilcoxon for the data with non-normal distribution. Pearson chi-square was used to measure qualitative variables. The percentage of changes in the severity of symptoms, based on the Conner's score, was evaluated by the Wilcoxon test for intra-group comparison and by the Mann–Whitney test for inter-group comparison. All statistical analyses were done by the program SPSS software version 19 for Windows (IBM Co., Armonk, NY, USA). *p* values less than 0.05 were considered significant.

RESULTS

There were 48 (87.8%) males and 2 (12.2%) females, with the mean age of 8.42 years who met the inclusion criteria and randomly enrolled in two groups of 25.

Demographic data, laboratory findings and CPRS results of subjects at the baseline are shown in Table 1. Although, no remarkable side effects were seen, but 3 patients in ferrous sulfate and 6 in the placebo group dropped out of the study. In ferrous sulfate group one was dis-

Table 1. Sample characteristics at the baseline

Characteristics	Ferrous sulfate (n = 25)	Placebo (n = 25)	*p* value
Age (yr)	8.09 ± 2.16	8.75 ± 3.09	0.470
Male sex	25 (100)	23 (92)	0.088
Height (cm)	124.82 ± 8.68	122 ± 27.07	0.693
Weight (kg)	28.18 ± 7.06	37.13 ± 24.04	0.052
Duration of disease (yr)	2.49 ± 2.25	4.19 ± 3.29	0.087
Family history of psychiatric disorders			0.401
Negative	17 (68)	17 (68)	
First degree	6 (24)	6 (24)	
Second degree	2 (8)	2 (8)	
Comorbidities			0.058
Negative	21 (84)	19 (76)	
Asthma	4 (16)	4 (16)	
Glucose-6-phosphate dehydrogenase deficiency	0 (0)	2 (8)	
Methylphenidate dose (mg/d)[a]	20.45 ± 4.06	20.94 ± 4.55	0.910
Hematological values			
Hemoglobin (g/dl)	12.38 ± 0.78	13.08 ± 1.30	0.065
Mean cell volume (fL)	68.14 ± 17.57	73.03 ± 15.01	0.375
Serum iron (μg/dl)	57.36 ± 22.49	77.50 ± 35.61	0.058
Serum ferritin (ng/ml)	20.66 ± 7.59	21.09 ± 6.33	0.857
Total iron binding capacity (μg/dl)	356.81 ± 29.49	347 ± 22.70	0.273

Values are presented as mean ± standard deviation or number (%).
[a]Almost all patients were under the treatment of psychostimulant as soon as they were diagnosed, with 0.3 mg/kg/dose and titrated to the optimal dose, that was 20 mg/d in most cases.

continued because of constipation and nausea and 2 were dropped out not due to any medical reasons. In placebo group, 3 patients were dropped out due to the same reason. There was no significant difference in dropouts from the completers in terms of age, sex, and severity of symptoms.

Serum ferritin levels in ferrous sulfate group increased from 20.66 ± 7.59 ng/ml at the baseline to 46.86 ± 25.53 ng/ml at the twelfth week, which was significantly more than the placebo group, from 21.09 ± 6.33 to 32.14 ± 9.37 ng/ml (p = 0.007). Iron status changes in both groups, from baseline to the 12th week, are shown in Table 2.

At the beginning of the project, most of the subscales of the CPRS had no significant clinical difference between the two groups; only the mean score of the psychosomatic subscale had a statistically significant difference between the groups (p = 0.038). The HI score had also no significant difference between the groups (p = 0.903).

In the sixth week, only the mean score of the psychosomatic subscale had a significant difference between the groups (p = 0.008). The two groups had no significant difference in HI scores (p = 0.460).

In the twelfth week, the mean score of conduct problems subscale had a significant difference between the groups (p = 0.012). The HI scores had no significant difference between the two groups (p = 0.401). The compar-

Table 2. Effect of treatment on Hematological values from baseline to endpoint at 12 weeks

Hematological values	Ferrous sulfate (n = 22)		Placebo (n = 19)		p value
	Mean ± SD	95% CI	Mean ± SD	95% CI	
Hemoglobin (g/dl)	−0.5 ± 1.30	− 0.62 to 0.53	1.13 ± 1.18	0.44 to1.81	0.037
Mean cell volume (fL)	−10.46 ± 16.17	−17.63 to −3.29	3.91 ± 10.69	−2.26 to 10.09	0.001
Serum iron (μg/dl)	−31.36 ± 33.01	−46.00 to −17.73	4.14 ± 21.05	−8.01 to 16.29	0.001
Serum ferritin (ng/ml)	−26.20 ± 20.45	−35.26 to −17.13	11.05 ± 5.97	−14.23 to −7.87	0.007
Total iron binding capacity (μg/dl)	23.45 ± 20.52	14.36 to 32.55	4.38 ± 21.65	15.91 to 7.16	0.000

SD, standard deviation CI, confidence interval.

Table 3. Comparison of mean CPRS subscales' scores from baseline to the endpoint at 12th week

CPRS subscales	Ferrous sulfate (n = 22)		Placebo (n = 19)		p value
	Mean ± SD	95% CI	Mean ± SD	95% CI	
Week 1					
Conduct	64.91 ± 11.38	59.87−65.95	69.14 ± 12.97	61.66−76.63	0.310
Learning	64.82 ± 14.56	58.36−71.27	61.29 ± 8.18	56.56−66.01	0.415
Psychosomatic	63.73 ± 20.19	54.78−72.68	50.71 ± 12.46	43.52−57.91	0.038
Hyperactivity/irritability	64.73 ± 9.53	60.50−68.95	62.00 ± 9.72	56.39−67.61	0.412
Anxiety	54.64 ± 8.27	50.97−58.30	52.86 ± 5.59	49.63−56.08	0.484
Hyperactivity index	64.55 ± 9.86	60.17−68.92	64.14 ± 9.09	58.90−69.39	0.903
Week 6					
Conduct	62.00 ± 12.28	56.55−67.45	63.50 ± 8.05	59.21−67.79	0.673
Learning	60.73 ± 15.33	53.93−67.53	64.38 ± 6.39	60.97−67.78	0.377
Psychosomatic	68.27 ± 20.20	59.31−77.23	52.38 ± 11.82	46.08−58.67	0.008
Hyperactivity/irritability	59.55 ± 8.66	55.71−63.38	58.25 ± 8.77	53.57−62.93	0.652
Anxiety	53.27 ± 6.30	50.48−56.06	54.50 ± 7.10	50.72−58.28	0.577
Hyperactivity index	61.00 ± 9.62	56.73−65.27	63.13 ± 7.11	59.34−64.91	0.460
Week 12					
Conduct	56.64 ± 9.19	52.56−60.71	66.63 ± 14.12	59.10−74.15	0.012
Learning	62.73 ± 15.98	55.64−69.81	62.25 ± 16.02	53.71−70.79	0.928
Psychosomatic	57.80 ± 16.73	49.15−68.10	58.63 ± 17.78	57.39−65.52	0.887
Hyperactivity/irritability	61.45 ± 9.17	57.39−65.52	62.13 ± 11.18	56.17−68.08	0.840
Anxiety	55.91 ± 9.57	51.67−60.15	52.13 ± 5.52	49.18−55.07	0.165
Hyperactivity index	63.00 ± 9.90	58.61−67.39	66.25 ± 13.72	58.94−73.56	0.401

CPRS, Conners' Parent Rating Scale; SD, standard deviation; CI, confidence interval.

ison of mean CPRS subscales' scores from baseline to the endpoint at 12th week is shown in Table 3.

To examine the trend of changes in the mean CPRS subscales' scores within the groups and between the groups, the percent change of scores were evaluated. The results are shown in Table 4. From the baseline to the sixth week after taking ferrous sulfate/placebo, the scores in conduct subscale problems of the placebo group ($p = 0.012$), and Hyperactivity/irritability subscale problems of both groups ($p = 0.034$ in ferrous sulfate, $p = 0.049$ in placebo) were improved significantly. The learning subscale score in the placebo group was declined significantly ($p = 0.012$). In the comparison of score changes between the groups, only the changes in the mean score of learning problems subscale were significantly different between the two groups (improved in the ferrous sulfate group compared with the placebo group, $p = 0.007$). There was no other significant difference in score changes of other subscales and HI in both intragroup and intergroup comparison in this period.

From the sixth to twelfth week after taking the ferrous sulfate/placebo, the mean scores of conduct and psychosomatic subscale in the ferrous sulfate group were improved significantly ($p = 0.030$ and $p = 0.050$, respectively). Additionally, the score of the psychosomatic subscale in the placebo group was declined significantly ($p = 0.021$). In the comparison of score changes between the groups, the changes in mean scores of conduct ($p = 0.023$) and psychosomatic ($p = 0.018$) subscales were significantly different between the two groups (improved in the ferrous sulfate group compared with the placebo group). There was no other significant difference in score changes of other subscales and HI in both intragroup and intergroup comparison in this period.

From the baseline to the 12th week almost all CPRS subscales improved in the ferrous sulfate group, and only the changes in conduct subscale scores were significant ($p = 0.003$). In intergroup comparison, there was no significant difference in score changes between two groups in none of CPRS subscales and HI.

Table 4. The effect of treatment on the percentage change[a] of the mean CPRS subscales' scores from baseline to the endpoint

CPRS subscales	Ferrous sulfate (n = 22)			Placebo (n = 19)			*p* value[c]
	Mean ± SD	95% CI	*p* value[b]	Mean ± SD	95% CI	*p* value[b]	
Week 1−6							
Conduct	−2.94 ± 19.42	−11.55 to 5.67	0.228	−6.17 ± 7.46	−10.48 to −1.86	0.012	0.396
Learning	−5.35 ± 15.65	−12.29 to 1.59	0.085	7.59 ± 9.76	1.96 to 13.23	0.012	0.007
Psychosomatic	9.95 ± 25.83	−1.5 to 21.41	0.193	11.63 ± 35.97	−9.14 to 32.40	0.673	0.895
Hyperactivity/irritability	−6.89 ± 13.61	−12.92 to 7.95	0.034	−7.66 ± 15.30	−16.50 to 1.17	0.049	0.412
Anxiety	−1.60 ± 9.83	−5.96 to 2.76	0.240	1.48 ± 11.61	−5.22 to 8.18	0.794	0.360
Hyperactivity index	−3.94 ± 17.56	−11.73 to 3.84	0.202	−2.20 ± 9.22	−7.52 to 3.13	0.424	0.948
Week 6−12							
Conduct	−8.08 ± 15.69	−10.48 to −1.86	0.030	6.57 ± 15.50	−2.38 to 15.52	0.324	0.023
Learning	2.85 ± 18.29	−5.26 to 10.96	0.585	−6.57 ± 20.34	−18.31 to 5.17	0.360	0.268
Psychosomatic	−15.46 ± 31.91	−30.40 to −0.53	0.050	10.40 ± 19.76	−1.01 to 21.81	0.021	0.018
Hyperactivity/irritability	3.55 ± 9.94	−0.86 to 7.95	0.122	7.45 ± 14.48	−0.91 to 15.81	0.096	0.101
Anxiety	4.05 ± 10.95	−0.80 to 8.91	0.070	−3.32 ± 17.40	−13.37 to 6.72	0.478	0.165
Hyperactivity index	2.42 ± 12.95	−3.32 to 8.16	0.078	5.36 ± 17.09	−4.51 to 15.33	0.307	0.172
Week 1−12							
Conduct	−11.02 ± 15.42	−17.86 to 11.30	0.003	0.40 ± 18.87	−10.49 to 11.30	0.825	0.151
Learning	−2.51 ± 16.02	−9.61 to 4.60	0.165	1.02 ± 22.98	−12.24 to 14.29	0.812	0.363
Psychosomatic	−5.59 ± 23.13	−16.41 to 5.24	0.216	22.03 ± 47.99	−5.68 to 45.84	0.167	0.119
Hyperactivity/irritability	−3.34 ± 17.62	−11.15 to 4.47	0.311	−0.22 ± 18.14	−10.69 to 10.36	0.637	0.696
Anxiety	2.45 ± 9.61	−1.81 to 6.72	0.192	−1.84 ± 13.18	−9.45 to 5.77	0.878	0.289
Hyperactivity index	−1.52 ± 14.27	−7.85 to 4.80	0.476	3.16 ± 16.33	−6.27 to 12.59	0.430	0.153

CPRS, Conners' Parent Rating Scale; SD, standard deviation; CI, confidence interval.

[a]Percentage change of the mean score (that represents the degree of change over time) were calculated by subtracting week 1 mean scores from week 6, week 6 from week 12 and week 1 from week 12, thendivide by the first score and multiply the answer by 100 thus a negative score indicated an improvement in the scales (the higher scores indicate the high severity of the diseases). [b]Intragroup comparison of the mean percentage change. [c]Intergroup comparison of the mean percentage change.

Generally, oral ferrous sulfate therapy was well tolerated in all patients. None of them had decreased appetite or adverse reactions. Constipation in 2 patients (9%) and alternate abdominal pain in 3 patients (13.6%) were reported, that were eliminated despite the constant use of ferrous sulfate during twelve weeks. Four patients (18.1%) had increased appetite while taking ferrous sulfate capsules. In the placebo group, 4 patients (19.21%) had gastrointestinal upset and abdominal pain and 2 patients (10.5%) complained from an increased appetite. No case of constipation or other adverse reactions was found in placebo group. In addition, vital signs and weight had not any significant clinical changes in both groups, within twelve weeks.

DISCUSSION

Iron is an essential and effective ingredient in the formation of myelin sheaths, synthesis of transducers, and neuronal metabolism. It is a cofactor of many enzymes and involves in the structure and transportation of brain proteins. The most common micronutrient deficiency in the world is iron deficiency [7,8]. Iron deficiency leads to poor myelination of the nervous system and disruption in the metabolism of monoamines. These changes not only affect memory, learning abilities, and motor skills but also cause psychological and mental disorders, especially in children [11]. About 10 studies have indicated the lower serum ferritin levels in ADHD patients than healthy controls [24]. Studies of Adisetiyo *et al.* [34], Menegassi *et al.* [35], and Calarge *et al.* [36] revealed a difference in dietary calorie and iron intake in ADHD patients compared with non-ADHD subjects.

In the present study, 50 patients with ADHD and serum ferritin levels lower than 30 ng/ml met the inclusion criteria and randomly entered into two groups. After twelve weeks, as expected, all hematological values were improved significantly in the ferrous sulfate group. Similarly, in Konofal *et al.* [37] study which the serum ferritin levels increased from 29.1 ± 17.6 ng/ml at baseline to 45.9 ± 22.6 ng/ml at 4th week and 55.7 ± 20.4 ng/ml at twelfth week in the iron treatment group ($p < 0.001$).

In this clinical trial study twelfth week, the mean CPRS score of conduct problems in the ferrous sulfate group was significantly lower than the corresponding score in placebo ($p = 0.012$).

In the evaluation of score changes, many significant improvements appeared in different CPRS subscales of ferrous sulfate group in different periods (Hyperactivity/irritability in the first six weeks, conduct and psychosomatic in the second six weeks, and conduct subscale from baseline to the endpoint). The reason is unclear; it needs further investigations to explore the exact cause. In intergroup comparison, the score changes of learning subscale in the first six weeks, and the score changes of conduct and psychosomatic subscale in the second six weeks were significantly improved in the ferrous sulfate group compared with the placebo group. Additionally, all subscales of the CPRS (except anxiety) were improved in the ferrous sulfate group from the baseline to the endpoint, however not statistically significant. All these results support the hypothesis that Iron supplementation may help the improvement of ADHD symptoms especially in conduct subscale. It is crucial to mention that a larger sample size could have yielded more accurate results. Also, given that the CPRS score in conduct subscale had improvement in all periods and the corresponding improvement was significant in the evaluation of baseline to the endpoint, it is possible that iron and ferritin levels may play a role, specifically in the conduct problems, a subscale that is fairly indicative of some problems such as arrogance, irritability, bullying or threatening others, physical fights, stealing, hurting animals and humans. Therefore, further studies are needed to assess their possible role. There is not any significant difference between ferrous sulfate and placebo groups in other hematological values except the serum iron level, that showed a marginal difference in the Table 1, and it seems that the CPRS subscales improvements could not be affected by this marginal baseline difference. Besides, the trend of changes in CPRS subscales is evaluated in both intergroup and intragroup comparisons; Nevertheless, it is important to mention biased sample probability.

In a similar study by Konofal *et al.* [37], the CPRS total score improved more in the iron group (−7.0 ± 14.0, $p = 0.055$) than the placebo group (−3.2 ± 22.8, $p = 0.769$). However, it didn't reach a significant level. The ADHD Rating Scale decreased significantly in the iron group after 12 weeks (−10.2 ± 14.0, $p = 0.008$). In another study by Sever *et al.* [38], on 14 patients with ADHD, a significant decrease in the CPRS score (from 17.6 ± 4.5 to 12.7 ± 5.4) was found after thirty days of treatment with Ferocal 5

mg/kg daily. Both of these studies were almost in line with ours.

Tolerance of oral ferrous sulfate was well in our patients. The side effects in our study (constipation and transient abdominal pain) were favorable with those reported in similar previous studies [30,37,38].

Our study had several limitations such as the small sample size of subjects, single assessment measure (CPRS) for assessing outcomes, lack of evaluation differences of iron on CPRS in different subtypes of ADHD and short duration of the study. On the other hand, it should be noted that serum ferritin may not represent iron levels in the brain. It is crucial to mention that the authors strongly believe that this study is a preliminary study. Therefore, further studies with larger sample size, longer follow up, multi assessment tool, and with more non-invasive methods, such as magnetic resonance imaging, to assess brain iron levels correctly is highly recommended. Moreover, several factors, such as dietary intake and comorbidities, have an effect on the serum iron level, that were not completely considered in our study. It is considered that nutritional status, weight and body mass index are closely related to hemoglobin level in the growing period of children. Because in children with ADHD, weight is an important factor in determining the dose of psychostimulant, so it might be necessary to specify the dose of psychostimulant taken between the two groups.

In conclusion, this study showed the promising effects of iron supplementation in the improvement of subscales of the CPRS, and the learning problems within the first six weeks, conduct and psychosomatic problems within the 2nd six weeks, and conduct problems in the twelfth week after intervention were improved in the ferrous sulfate group compared with the placebo group. Almost all CPRS subscales had improvement from the baseline to the endpoint (although not significant). Therefore, all these results confirm the need for further investigations with larger sample size and longer follow-up. Oral ferrous sulfate therapy had no significant side effects in treated patients.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Elham Bidabadi, Sepehr Tohidi, Maryam Kousha. Data acquisition: Sepehr Tohidi, Parham Mashouf, Mohammad-Javad Khosousi, Melika Amoukhteh. Formal analysis: Mohammad-Javad Khosousi, Melika Amoukhteh. Funding: Elham Bidabadi. Supervision: Elham Bidabadi, Maryam Kousha. Writing—original draft: Sepehr Tohidi, Parham Mashouf, Tamkin Shahraki. Writing—review & editing: Elham Bidabadi, Parham Mashouf, Tamkin Shahraki.

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