Original Articles

Impact of Iron Supplementation on Children with Severe Attention Deficit Hyperactive Disorder- A Randomized Clinical Trial

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Abstract

Background: *Iron acts as a risk factor and psychostimulant modulator in treatment of ADHD with iron deficiency anemia.*

Objective: *To see the impact of iron supplementation on severe ADHD children.*

Materials and Methods: *This randomized controlled trial conducted in the OPD, Pediatric Neurology from July 2019 to January 2020; NINS 50 children of severe ADHD with iron deficiency were enrolled. Participants were randomized into group A (25 cases) given a combination of Methylphenidate and iron, and group B (25 cases) given Methylphenidate alone for 3 months. Conner's rating scale, CBC and serum ferritin was evaluated after one and three months, severity was compared between treatment groups. Analysis of data was done by SPSS version of 22.0.*

Result: *Combined ADHD, poor academic performance, poor appetite, frequent infection was common features of IDA among the cases. All hematological parameters were increased from baseline to 1 month and 3 months follow up in all cases but significantly improved in Iron receiving groups. the severity of T scores of ADHD index were decreased at 1 month (p=0.047) and 3 months (p= 0.026) after intervention.*

Conclusion: *This study concluded that iron supplementation along with psychostimulant found better response in severe ADHD children*

Key words: *Iron deficiency anemia, Attention Deficit Hyperactive Disorder (ADHD), Corner's Parent rating scale*

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Introduction:

Attention deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of school age children is characterized by inattention, poor impulse control and decreased self-inhibitory capacity; motor over activity and motor restlessness.[1] It is estimated globally 9% of school aged children, 2-6% in adolescent and approximately 2% of adult have ADHD.[1] The prevalence shows rising trends in the recent years to about 11%.[2] ADHD is a final common pathway for a variety of complex brain developmental process with multifactorial etiology like genetic, environmental and nutritional factors.[1] Alterations in frontal-limbic-striatal and frontal-parietal-subcortical circuits leads to ADHD. Dopamine is an important neurotransmitter in these circuits.[3] Iron is a cofactor of enzymes in Dopamine metabolism,[4] low iron decreases dopamine transporter expression,[5] may lead to dysfunction in the basal ganglia,[6] iron deficiency has been reported in children with cognitive and behavioral impairments that prominently include poor attention and hyperactivity.[7]

The goal of ADHD treatment is to improve symptoms, optimize functional performance and remove behavioral obstacles.[8] Evidence-based treatments for ADHD include pharmacological, psychosocial/behavioral therapies, psychoeducational intervention and combined therapy. Recently, the potential effect of environmental (non-genetic) factors has attracted attention in ADHD.[9]

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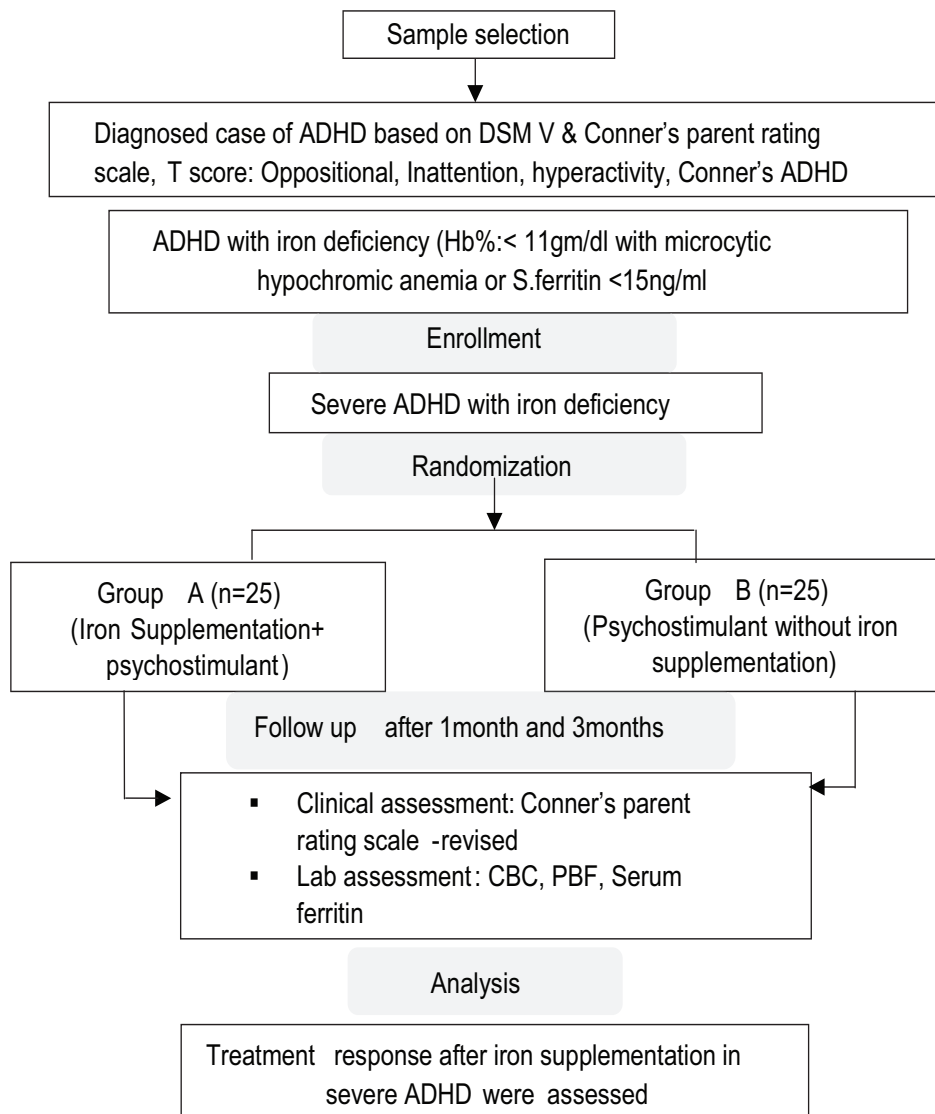5. Prof. Pediatrics Neurology, NINS

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Environmental factors are potentially modifiable and may represent preventable targets for these disorders, such as iron supplementation.[10] The aim of this study was to find out the impact of iron supplementation on severe ADHD children.

Materials and methods:

A randomized controlled trial was done from July 2019 to January 2020 in Outpatient Department, Pediatric neurology, National Institute of Neuroscience and Hospital. Fifty children aged 3-17 years with ADHD according to DSM 5 and clinically anemic were enrolled in this study. After enrollment children were clinically evaluated thoroughly by taking history related to age at onset, type and severity of ADHD, academic performance, social factor, family history, socioeconomic status, parental educational status, developmental history, and dietary history were taken. Features of iron deficiency (fatigability, dizziness, poor appetite, dysphagia, pica, history of frequent infection, palpitation) were also recorded. For further evaluation of ADHD, Conner's rating was done by child psychologist. According to T score of Conner's rating scale patients were categorized as severe ADHD groups. In addition, complete blood count with peripheral blood film, serum ferritin level was done in every case at baseline. There after severe ADHD with iron deficiency anemia cases were randomized into two allocated groups, group A and group B. Randomization was done by lottery method. Data were collected by predesigned structured questionnaire

Sample selection

Diagnosed case of ADHD based on DSM V & Conner's parent rating scale, T score: Oppositional, Inattention, hyperactivity, Conner's ADHD

ADHD with iron deficiency (Hb%:< 11gm/dl with microcytic hypochromic anemia or S.ferritin <15ng/ml

Enrollment

Severe ADHD with iron deficiency

Randomization

Group A (n=25)
(Iron Supplementation+ psychostimulant)

Group B (n=25)
(Psychostimulant without iron supplementation)

Follow up   after 1month and 3months

- Clinical assessment: Conner's parent rating scale -revised
- Lab assessment: CBC, PBF, Serum ferritin

Analysis

Treatment response after iron supplementation in severe ADHD were assessed

All the cases received methylphenidate (Ritalin) 10mg/day for less than 25 kg and 20 mg/day for >25 kg in two divided dose for 3 months. Along with methylphenidate group A also received iron 6mg/kg/day in two divided dose. All cases were advised for iron rich diet and anti-helminthic medication. Follow up assessment by parents Conner's rating scale and physical examination (weight, pulse, BP) were done at 1 month and 3 months of treatment. CBC, blood film, serum ferritin level was assessed after 1 and 3 months of initial treatment to evaluate iron restoration. After 3 months of treatment, primary end point of the study was to find out the impact of iron among severe ADHD cases as per allocated regime and core symptoms of ADHD.

Data analysis was performed with SPSS software, versions 22.0. Continuous data that were normally distributed was summarized in mean, standard deviation, median, minimum and maximum. Skewed data was presented in the maximum, upper quartile, median, lower quartile, minimum and number of observations. Categorical or discrete data was summarized in frequency counts and percentages. For end points analysis, chi square test was used for categorical variables and an analysis of variance (one-way ANOVA Test) for continuous outcomes. A two-sided P value of less than 0.05 was considered to indicate statistical significance. The primary and secondary efficacy analyses was performed according to the intention-to-treat principle. After enrollment informed consent was taken from parents or caregivers of the child and ethical approval was taken from ethical review committee of National Institute of Neurosciences and Hospital.

Result:

Among 50 severe ADHD cases mean age was 6.4 ± 2.26 years in group A and 5.86 ± 1.96 years in group B (p=0.349), most were male, (M: F=4:1) in group A and (M: F =5:1) in group B. There was no significant difference between the two treatment groups of severe ADHD in socioeconomic status and parental educational level [Table-I]. Combined ADHD was the prominent category, poor academic performance, poor appetite, frequent infection, inadequate feeding was found common features of IDA cases but no significant

difference was found among severe ADHD groups [Table-II].

All the hematological parameters showed incremental response among the study cases. All hematological parameters were improved in both groups but improvement was more in group A than group B from baseline to 1 month and 3 months follow up. Hb%, Hct, MCH, serum ferritin significantly improved in group A than group B from baseline to 3 months follow up [Table-III].

Table-I
Demographic profile among Severe ADHD groups (N=50)

	Group A (n=25) (MPH + Iron)	Group B (n=25) (MPH)	P value*
Age (years)	6.4±2.26	5.86±1.96	0.349
Gender (M/F)	20/5 (4:1)	21/4 (5:1)	0.500
Socioecon. status			
Poor	6 (24%)	2(8%)	
Middle	11 (44%)	14 (56%)	0.441
Good	8 (32%)	9 (36%)	
Maternal education			
Illiterate	0 (0%)	2 (8%)	
Primary	3 (12%)	3 (12%)	0.528
Secondary	12 (48%)	12 (48%)	
Graduate	10 (40%)	8 (32%)	
Paternal education			
Illiterate	1(4%)	1(4%)	
Primary	2 (8%)	4 (16%)	0.828
Secondary	10 (40%)	8 (32%)	
Graduate	12 (48%)	12 (48%)	

Qualitative data: chi square test and quantitative data: one-way ANOVA test

Table-II
Clinical characteristics among Severe ADHD (N=50)

Variable	Group A (n=25) (MPH + Iron)	Group B (n=25) (MPH)	P value*
ADHD (DSM V)			
Inattention	0 (0%)	0 (0%)	
Hyperactivity-impulsivity	1(4%)	4 (16%)	0.174
Combined	24(96%)	21(84%)	
Academic performance			
Poor	15 (60%)	18 (72%)	0.640
Medium	8 (32%)	6 (24%)	
Good	2 (8%)	1 (4%)	
Features of iron deficiency anemia			
Poor appetite	18 (72%)	14 (56%)	0.189
Frequent infection	8 (32%)	10 (40%)	0.384
Inadequate feeding	6 (24%)	5 (20%)	0.500
Pica	2 (8%)	1 (4%)	0.500
Dizziness	1 (4%)	0 (0%)	0.500
Fatigue	0 (0%)	1 (4%)	0.500
Dysphagia	0 (0%)	2 (8%)	0.245

*Chi square test

T score of different domains in Conner's rating scale among the study cases showed decremental response from baseline. Oppositional T score fall from baseline (73.48 ± 11.16) to 1 month (67.20 ± 9.40) and 3 months (57.16 ± 10.03) follow up in group A, similar fall was noted in group B from baseline (67.64 ± 11.74), p=0.078 to 1 month (64.92 ± 10.98), p= 0.436 and 3 months (59.16 ± 8.87), p=0.459. Cognition was improved in both group A and group B among severe ADHD children as T score of cognitive function was found falling from baseline [group A: 76.52 ± 9.51, group B: 77.48 ± 8.70; p=0.712] to 1 month [group A: 67.40 ± 11.81, group B: 75.84 ± 8.43; p=0.06] and 3 months [group A: 58.36 ± 13.06, group B: 65.00 ± 11.89; p=0.06] follow up. These also found statistically insignificant. Hyperactivity T score was also falling, at 3 months this decrement was more in group A (from 82.48 ± 7.32 to 58.20 ± 9.27) than group B (from 78.32 ± 8.38 to 65.16 ± 9.64) and found statistically

significant (p= 0.012). Decremented response was also noted in ADHD index T score among severe ADHD cases and more in group A [baseline: 76.72 ± 7.27, 1 month: 67.44 ± 8.74 and 3 months: 56.28 ± 10.4] than group B from baseline to 3 months follow up (p= 0.01).

Table-III
Hematological parameters among Severe ADHD cases

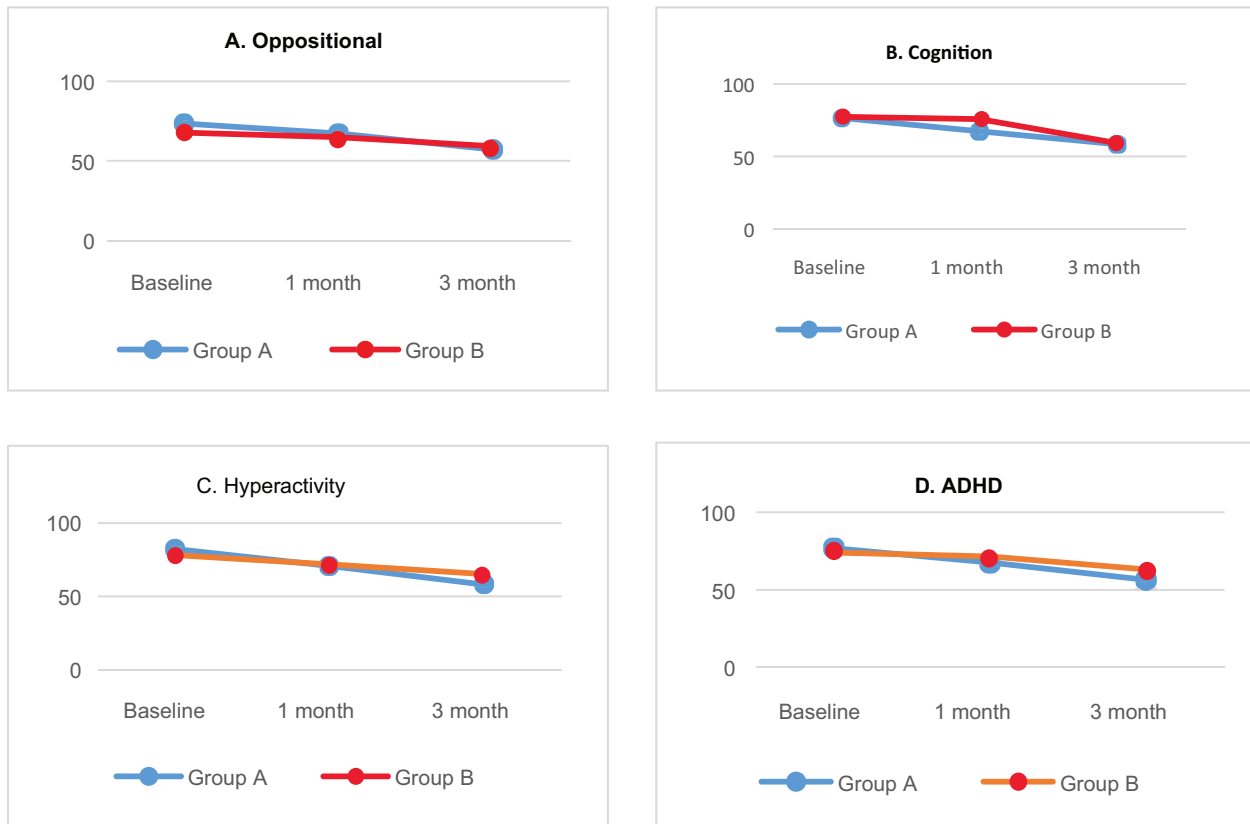| Hematological profile	Group A (MPH + Iron)	Group B (MPH)	P value*
Hb %			
Baseline	10.76 ± 0.55	10.82 ± 0.54	0.664
1 month	11.97 ± 0.75	11.87 ± 0.85	0.664
3 month	12.45 ± 0.80	11.72 ± 0.71	**0.002**
Hct			
Baseline	0.30 ± 0.047	0.30 ± 0.044	0.927
1 month	0.35 ± 0.03	0.33 ± 0.03	**0.021**
3 month	0.36 ± 0.02	0.34 ± 0.02	**0.004**
PCV			
Baseline	61.98 ± 10.70	71.68 ± 10.32	0.02
1 month	74.53 ± 8.86	746.40 ± 7.76	0.432
3 month	76.66 ± 7.41	77.06 ± 6.06	0.839
MCH			
Baseline	24.76 ± 1.90	24.26 ± 1.90	0.546
1month	26.07 ± 1.78	26.07 ± 1.78	**0.000**
3 month	27.03 ± 1.91	26.98 ± 1.81	**0.000**
MCHC			
Baseline	31.66 ± 2.07	31.72 ± 1.84	0.903
1 month	33.10 ± 0.97	33.05 ± 0.63	0.823
3 month	33.70 ± 1.37	34.28 ± 1.90	0.236
RDW			
Baseline	14.88 ± 1.37	13.61 ± 1.62	0.04
1 month	12.71 ± 1.96	12.06 ± 1.75	0.236
3 month	11.59 ± 2.06	11.37 ± 1.57	0.680
Serum Ferritin			0.289
Baseline	12.27 ± 8.68	14.76 ± 7.65	
1 moth	33.10 ± 19.86	29.52 ± 12.10	0.450
3 month	56.65 ± 23.62	43.98 ± 20.75	**0.044**

*One-way ANOVA test

Figure 1: Changing pattern of T score of Conner's rating scale among the study cases

Discussion

In this study baseline demographic profile of both groups of severe ADHD were comparable. Mean age was 6.4 ± 2.26 in group A (iron supplementation group) and 5.86 ± 1.96 in group B of severe ADHD and male were predominant than female in both groups, which was similar to a study by Venkatesh et al. who reported mean age as 5.7 years.[11] Another study found that the highest prevalence (29.2%) of ADHD among 11-12 years and 5.2% in children of 3-4 years[12] which was not comparable with this study, may be due to difference in diagnostic criteria used for ADHD. While ADHD may be diagnosed in very young children, as suggested in the DSM 5. Polanczyk et al.[13] also observed that ADHD was more frequent in male than in female, with an estimated ratio 2:1 or higher, which may account for markedly higher treatment referral rates among boys. Another study also reported that males are 3 times more likely to have ADHD than females and exhibit the predominantly hyperactive or combined type.[14]

Present study found that most of the patient belongs to middle socioeconomic status with educated parents (Table-I). One study found similar result and the authors hypothesize that, higher rates of ADHD observed in affluent families likely represent an effort by educated parents to seek help for their children who may not fulfilling their expectation for schoolwork.[15]

In this study, combined type of ADHD was the prominent features in both groups of severe ADHD with poor academic performance and common features of IDA were poor appetite and frequent infection in all groups (Table-II). JUNEJA, et al.[16] also found similar findings. They concluded that iron deficiency might contribute to the symptoms of ADHD and iron deficient children may have more severe manifestations. One study suggested that preschool-aged children are commonly presented with inattention and hyperactive behavior. From childhood to adolescence, inattention becomes more prominent, whereas hyperactivity tends to shift from impulsive, disinhibited behavior to feelings of restlessness or impatience.[17] Murray et al.[18] in their study over 4 years period reported that

51% of children showed a reliable decline in academic performance in ≥1 subject, with 20% having a reliable decline in academic performance in ≥2 areas.

All hematological parameters were increased from baseline to 1 month and 3 months follow up in all cases but significant improved was found in iron supplementation groups (group A) and all domain of conner's rating scale of ADHD were also improved in this group than group B. T score of different domains (oppositional, cognitive, inattention, ADHD index) in Conner's rating scale showed decremental response from baseline to 1 month and 3 month follow up and more decremental response found in iron supplementation group (Table-III, Figure-1). Konofal et al.[10] found significantly lower serum ferritin levels in ADHD children versus comparison group. Additionally, serum ferritin levels were significantly correlated with the Conner's Parent Rating Scale (CPRS) total and inattentive scores. Subsequently Oner's group[19] has published a series of studies that also support the role of iron deficiency in ADHD. They first reported a significant inverse correlation between serum ferritin levels and total scores on the CPRS. Therefore, like other studies described above, the present study also found the positive outcome with iron supplementation in severe ADHD in children. Similar finding was noted in a study by Chadi Calarge et al.[20] that ferritin concentration was negatively associated with scores on the Conner's Parent Rating Scale- Revised.

So this study concluded that iron supplementation with other intervention in severe ADHD may provide better outcome. Simple iron supplementation might make the treatment of ADHD more effective. A better understanding of relationship between ADHD and iron deficiency can be made if other parameter of iron indices is used as assessing tools. Not only the peripheral iron parameters but also the brain iron parameter will have a better search for causative link of iron deficiency with ADHD. There were some limitations as sample size was small and single center study, Un-blinded design. Other parameters of iron indices could not be assessed.

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