DOI: 10.7860/JCDR/2020/43748.14144

Case Series

Psychiatry/Mental Health Section

Study of Iron Profile and Effect of Oral Iron Supplementation in Patients of Attention Deficit Hyperactivity Disorder: A Case Series

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ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) is a neuropsychiatric condition affecting the preschoolers, children, adolescents and adults globally. Dopamine synthesis is dependent on availability of iron in the body and dopamine deficit theory is the widely accepted ADHD causation theory. So, serum iron levels are important to watch out for in patients suffering from ADHD. This article describes six cases to emphasise the importance of diagnosing and treating underlying Iron Deficiency (ID) state with oral iron supplementation for effective management of patients suffering from ADHD. All the six cases which were given oral iron supplementation along with methylphenidate had shown improvement in inattentive domain and in hyperactivity-impulsivity domain at both home as well as school settings. They were given doses of methylphenidate and oral iron supplement as per the recommended body weight. Their parents and teachers were asked to mark the responses on Swanson, Nolan, and Pelham Rating Scale (SNAP-IV) 26 item parent and teacher rating scale respectively. Scores on SNAP-IV were recorded at the first visit and after three months of treatment. Scores were then evaluated on both occasions for evidence of improvement in ADHD symptoms.

Keywords: Dopamine, Hyperactivity-impulsivity domain, Inattentive domain, Nolan and Pelham rating scale, Swanson

INTRODUCTION

ADHD affects children and adults globally. Symptoms manifest before age of 7 years according to Diagnostic and Statistical Manual of Mental disorders, fourth edition (DSM-IV) diagnostic criteria [1,2]. Children with ADHD tend to exhibit inattentive features like failure to sustain close attention in home or school, making mistakes at homework/schoolwork/other activities, difficulty in focusing attention during conversations, not following instructions appropriately, not able to complete and avoiding or disliking homework/schoolwork/other tasks that require sustained attention and frequently losing school material [1]. Children with hyperactivity or impulsivity type of ADHD tend to show features like frequent fidgeting or tapping or squirming movements while sitting, often leaving seat in situations where remaining seated is expected like often leaving place in the classroom or in office or in other workplace, often running or climbing in situations where it is inappropriate, unable to engage in leisure activities or play quietly, acting as if "driven by a motor", talking excessively and interrupting the conversations of other people, blurting out an answer before a question gets completed and having difficulty in waiting for his/her turn (example-while waiting in a line) [1]. To diagnose a child suffering from either or both types of ADHD, symptoms must persist for a period of at least six months [1,2]. Several inattentive or hyperactive-impulsive symptoms should be present in two or more settings (i.e., at home, school or work) [1]. Sufferers with ADHD frequently have significant impairment in academics and in interpersonal and social situations [1,2]. Iron is pre-requisite for dopamine synthesis in brain. Iron deficiency (ID) leads to dopamine deficit [3]. Dopamine synthesis is dependent on availability of iron in the body and dopamine deficit theory is the widely accepted ADHD causation theory. So serum iron levels are important to watch out for in patients suffering from ADHD.

CASE SERIES

Case 1

An eight-year-old boy was exhibiting symptoms at home like not paying close attention to his parents' instructions, doing mistakes in homework, and jumping and running inside house frequently. He talked excessively by asking multiple questions and interrupting others' conversation. He did not pay attention in classroom, making careless mistakes in schoolwork and losing his school items. He could not sit quietly, used to leave seat and go outside classroom. He interrupted children, while playing both at school during recess period and outside school campus. His behaviour was persistent since last three years, at school and at his home. He was diagnosed as ADHD, combined type according to DSM-IV diagnostic criteria by psychiatrist [1].

Following three months treatment with Methylphenidate and oral iron supplementation, there was improvement in blood parameters like Haemoglobin (Hb), Mean Corpuscular Volume (MCV), serum iron and serum ferritin, which were altered at first visit. Other blood parameters remained within normal range. Following three months treatment, there was improvement in SNAP-IV 26 item teacher and parent rating scale scores [4]. The scores suggested that the severity of ADHD reduced from severe to mild level. The summary of changes in blood parameter values, changes in SNAP-IV scores and doses of methylphenidate and oral iron supplementation is presented in [Table/Fig-1,2].

Case 2

An eight-year-old girl was accompanied by her parents complaining about lack of attention and difficulty in studies (mistakes in doing academic home works etc.). She did not pay attention towards teachers when they talk with her. She started making mistakes while doing school work, avoided school work, used to lose her attention while reading books and often lose her school material like pencils, eraser, notebooks, etc. There were no symptoms suggestive of hyperactivity-impulsivity. Symptoms of inattentiveness were persistent since last two years. She was diagnosed as ADHD,

Patient number	Blood parameters*	Values of blood parameters		SNAP-IV scores							
				At first visit				After three months treatment			
				Teacher		Parent		Teacher		Parent	
		At first visit	After three months treatment	I	H	I	H	I	H	I	H
1	Hb (gm %)	12.2	13.2	25	24	26	23	17	14	16	14
	MCV (cubic-micron)	79	88								
	MCH (pico-gram)	26.6	32.5								
	MCHC	30	34								
	RDW	11	11.2								
	Serum Iron (µg/dL)	73	119								
	Ferritin (ng/ml)	14	78.5								
	TIBC (µg/dL)	220	276								
2	Hb (gm %)	11.3	13.1	23	7	24	4	18	5	13	3
	MCV (cubic-micron)	81	84								
	MCH (pico-gram)	28.5	29.4								
	MCHC	32	33.3								
	RDW	10	12								
	Serum Iron (µg/dL)	78	122								
	Ferritin (ng/ml)	13	100								
	TIBC (µg/dL)	247	335								
3	Hb (gm %)	13.2	14.0	14	23	19	25	11	17	9	15
	MCV (cubic-micron)	75	82								
	MCH (pico-gram)	27	31.8								
	MCHC	31.3	34.2								
	RDW	10.8	14.7								
	Serum Iron (µg/dL)	59	108								
	Ferritin (ng/ml)	102	178								
	TIBC (µg/dL)	217	302								
4	Hb (gm %)	13.4	15	8	23	9	26	6	13	4	11
	MCV (cubic-micron)	83	86								
	MCH (pico-gram)	23.1	32.2								
	MCHC	30.7	32.9								
	RDW	11.3	13.7								
	Serum Iron (µg/dL)	69	117								
	Ferritin (ng/ml)	98	187								
	TIBC (µg/dL)	303	379								
5	Hb (gm %)	13.1	14.4	22	24	17	23	8	13	10	16
	MCV (cubic-micron)	72	82								
	MCH (pico-gram)	26.7	31.3								
	MCHC	31.9	34.6								
	RDW	8.7	14								
	Serum Iron (µg/dL)	102	127								
	Ferritin (ng/ml)	12	134								
	TIBC (µg/dL)	277	322								
6	Hb (gm %)	13.1	14.8	25	10	23	12	14	7	15	8
	MCV (cubic-micron)	80	84								
	MCH (pico-gram)	28.2	29.9								
	MCHC	31.1	32.4								
	RDW	11	12								
	Serum Iron (µg/dL)	60	110								
	Ferritin (ng/ml)	14	128								
	TIBC (µg/dL)	223	298								

[Table/Fig-1]: Case-wise blood parameters and SNAP-IV scores distribution at first visit and after three months of treatment.
Hb: Haemoglobin; MCV: Mean corpuscular volume; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; RDW: Red cell distribution width; TIBC: Total iron binding capacity. I: Inattentive type of ADHD. H: Hyperactive-impulsive type of ADHD.
*Normal values of blood parameters: 1) Hb- 12 to 15.5 gm%; 2) MCV- 80 to 90 cubic-micron; 3) MCH- 26.5 to 33.5 pico-gram; 4) MCHC- 30 to 36.5%; 5) RDW- 10 to 15%; 6) Serum Iron-100 to 150 µg/dL; 7) Ferritin-22 to 322 nangoram/mL; 8) TIBC- 215 to 535 µg/dL

Patient number	Doses at first visit		Doses after three months treatment	
	Methylphenidate (mg/day)	Oral iron (mg/day of elemental iron)	Methylphenidate (mg/day)	Oral iron (mg/day of elemental iron)
1	10	60	30	60
2	10	60	20	60
3	10	60	30	60
4	10	60	30	60
5	10	60	20	60
6	10	60	30	60

[Table/Fig-2]: Patient-wise details regarding doses of Methylphenidate and oral iron supplementation at first visit and at three months of treatment.

predominantly inattentive type according to DSM-IV diagnostic criteria by psychiatrist [1].

Methylphenidate and oral iron supplementation therapy went on for three months; there was improvement in blood parameters like Hb, serum iron and serum ferritin, which were altered at first visit. Other blood parameters remained within normal range [Table/Fig-1,2]. Following treatment, there was improvement in SNAP-IV- 26 item teacher and parent rating scale scores [4]. The scores suggested that the severity of ADHD reduced from severe inattentive ADHD to moderate and mild inattentive ADHD as per the teacher and parent scores, respectively. Her academic performance showed improvement.

Case 3

A 10-year-old boy was behaviourally hyperactive, not able to sit quietly at one place, tapping limbs and squirming constantly and interrupting others during conversation at home. At home, he was inattentive towards his parents' instructions. In school, he was used to leave classroom during lectures and would run to another classroom interrupting others. He avoided reading and writing as he was not able to concentrate. He frequently got forgetful and used to leave belongings at school. He was lagging in studies. Since last five years his behaviour was persistent. He was diagnosed as ADHD, combined type according to DSM-IV diagnostic criteria by psychiatrist [1].

Methylphenidate and oral iron supplementation therapy was provided for three months. MCV and serum iron improved [Table/Fig-1,2]. According to SNAP-IV scale scores [4] the severity of hyperactivity-impulsivity domain of ADHD reduced from severe to mild severity. Also, there was improvement in inattentive domain and its severity dropped down to clinically insignificant level.

Case 4

A 12-year-old boy reported with his parents. The parents complained of the child of talking excessively and interrupting others during conversation and while at work. He could not sit quietly at one place and was always running around. Teachers were complaining about his hyperactive behaviour at school and that he was lagging in studies. His symptoms were persistent at home and school, since last six years. Diagnosis of ADHD predominantly, hyperactive-impulsive type was made according to DSM-IV diagnostic criteria by psychiatrist [1].

After methylphenidate and oral iron supplementation, there was improvement in blood parameters like Mean Corpuscular Haemoglobin (MCH) and serum iron level [Table/Fig-1,2]. Following three months treatment, according to SNAP-IV scale scores [4], severity of hyperactivity-impulsivity domain of ADHD reduced from severe to clinically insignificant level. Symptoms of inattentive domain of ADHD remained clinically insignificant.

Case 5

A nine-year-old boy exhibited hyperactivity. He talked excessively and did not pay attention at school and did not show interest in studies. He was hyperactive at school too and the teachers could not make him sit at one place. His symptoms were persistent since last three years at home and at school. Diagnosis of ADHD, combined type was made according to DSM-IV diagnostic criteria by psychiatrist [1].

Following three months treatment with methylphenidate and oral iron supplementation, there was improvement in MCV, Red Cell Distribution Width (RDW) and serum ferritin level [Table/Fig-1,2]. Following the treatment, according to SNAP-IV scale scores [4], severity of hyperactivity-impulsivity domain of ADHD reduced from severe to mild level. Severity of inattentive domain reduced from moderate (rated by teacher) and mild (rated by parent) to clinically insignificant level (rated by both teacher and parent).

Case 6

A 15-year-old boy at his home failed to pay attention to the conversation of family members and asked them to repeat their conversation with him. While trying to follow the requests of his family members, he would often forget about the task in the middle and was making mistakes in his academic tasks. At school he did not pay attention and made careless mistakes. While reading any text from a book he would lose focus. He got forgetful about his belongings. He was persistently exhibiting symptoms since the last nine years. Diagnosis of ADHD, predominantly inattentive type was made according to DSM-IV diagnostic criteria by psychiatrist [1].

Following three months treatment, there was improvement in blood parameter like serum ferritin level, which was altered at first visit. Other blood parameters remained within normal range [Table/Fig-1,2]. Following three months treatment, scores on SNAP-IV scale suggested that severity of inattentive symptoms of ADHD was reduced from severe to mild level [4]. While hyperactivity-impulsivity symptoms remained clinically insignificant.

[Table/Fig-1] shows case-wise distribution of blood parameters and SNAP-IV scale scores at first visit and after three months of treatment. Three cases had predominantly combined type of ADHD (i.e., inattentive and hyperactive-impulsive type), two had predominantly inattentive type of ADHD and one had predominantly hyperactive-impulsive type of ADHD. SNAP-IV-26 item teacher and parent rating scale were applied at first visit and after three months of treatment to assess change in ADHD severity. SNAP-IV scoring was done according to standardised cut-off scores. SNAP-IV scores of below 13 indicate clinically insignificant symptoms of both inattentive and hyperactive-impulsive domains of ADHD. While the scores of 13-17, 18-22 and 23-27 indicate mild, moderate and severe symptoms respectively for both domains of ADHD [4]. According to these scores on SNAP-IV, study participants were evaluated at first visit and after three months of treatment. Parental version of scale was solved by the parent, while teacher version was solved by class teacher of each child. During visits, a copy of SNAP-IV was given to parent so that they could give it to teacher and bring back those filled version to the treating psychiatrist. This method was followed at first visit and after three months of treatment.

DISCUSSION

Above cases highlight an importance of assessing Complete Blood Count (CBC) and serum iron profile in patients of ADHD. In the current case series, majority i.e., 5 out of 6 participants were boys. Half of the children had combined type of ADHD as per DSM-IV diagnostic criteria. Second most common type of ADHD was predominantly inattentive type and least common type was predominantly hyperactive-impulsive type of ADHD. On CBC, five children had low serum iron, four had low serum ferritin, three had low MCV, and one had low MCH and low RDW. Prevalence of ID among Indian children is around 70%, and its correlation to presence and severity of ADHD is important issue [5]. If such relationship is established, correcting ID may lead to improvement

in ADHD symptoms. For diagnosis of ID, a systematic review study observed that all the studies they reviewed had recommended measurement of serum ferritin concentrations [6].

According to four guidelines, 12 to 15 µg/L is the proposed threshold for ferritin in children to define ID [7-10]. Hallberg L et al., and Milman N et al., have defined ID as serum ferritin concentration of <15 µg/L [11,12]. According to World Health Organisation (WHO) criteria for diagnosing ID, serum ferritin has the highest success rate (90%) followed by body/serum iron stores (78%) [13]. So, WHO diagnostic criteria were used for the diagnosis of ID in present study.

In the present case series, there was improvement in all these blood parameters on treatment with oral iron supplementation. Oral iron supplementation was given simultaneously with methylphenidate which had led to improvement not only in blood parameters but in ADHD symptoms also which is evident in [Table/Fig-1] and discussed in individual cases. Methylphenidate was given simultaneously along with oral iron supplementation to all participants as per WHO 2016 Guideline [14]. In the present study, CBC and serum iron profile in six patients at first visit and after three months of treatment were assessed. Methylphenidate was given as per the body weight of study participants keeping in view of maximum approved dose of 2 mg/kg per day, and dose was titrated in all the six cases to find an effective dose in them. Maximum effective dose of methylphenidate is 30 mg/day [15].

Meta-analysis from 2012 using DSM-IV criteria, the prevalence of ADHD was 5.9-7.1%, with higher prevalence among boys [2]. This was similar to present study finding where boys had outnumbered girls. In present study, all the children with ADHD had deranged iron profile. An Indian study had found significant correlation between body iron status and ADHD symptoms [5]. Parisi P and Cortese S, found no association of serum ferritin levels with ADHD. But they concluded that if we rely on serum ferritin alone, we might miss opportunity to find out true relationship between low iron status and ADHD. Therefore, they advised to move beyond serum ferritin levels [16]. Juneja M et al., found that serum ferritin levels were significantly lower in children with ADHD compared to controls [5]. Waknine Y, observed that serum ferritin levels were significantly low in children with ADHD compared with controls [17]. He also observed that low serum ferritin levels correlated with more severe general scores on Conners' Parent Rating Scale. He concluded that iron supplementation could be considered as first-line treatment of ADHD and ID, adding that such therapy may lead to improvement in central dopaminergic activity and may decrease need for psychostimulant medications [17]. Islam K et al., found that Hb, iron, ferritin, MCV and MCH were lower among cases and negatively correlated to ADHD, while reverse was for Total Iron Binding Capacity (TIBC) and ADHD. They concluded that ID was significantly associated with ADHD [18]. Millichap JG et al., didn't find any significant lowering of serum ferritin levels among children with ADHD [19]. This finding may suggest that ID may not be the universal finding among children with ADHD [19]. Kwon HJ et al., observed significant difference for MCV, MCH and TIBC levels among children with ADHD [20]. Similar to present study findings and Kwon HJ et al., finding, Islam K et al., observed that there was strong correlation of ADHD with Hb, ferritin, TIBC, MCV, MCH and ID. But they didn't studied different types of ADHD [18].

From literature, it has been evident that children with Restless Leg Syndrome (RLS), and a subset of children with ADHD, may share a common dopaminergic deficit. From available study finding, it was evident that 44% of the patients with ADHD had RLS symptoms or RLS, while up to 26% of the patients with RLS had ADHD symptoms or ADHD [21]. Future studies should focus on whether treating RLS leads to improvement in ADHD symptoms.

Limitation(s)

There are few limitations of the present series analysis. When ID occurs as comorbidity in ADHD, sleep might get hampered and sleep pattern as well as quality of sleep were not assessed in the present study. Another limitation is that ID has been found to cause RLS in all age groups including the children which itself might be the reason for poor sleep quality which was not assessed in present study. Third limitation is that keeping in view of the higher prevalence of ID among Indian children a well-designed case control study would be more informative and productive regarding the comparative role of methylphenidate treatment and oral iron supplementation among children with ADHD.

CONCLUSION(S)

Assessment of children with ADHD for ID is important task. ID among Indian children is widely spread. Oral iron supplementation could be considered as one of main strategies for management of children suffering from ADHD and ID along with methylphenidate for better outcome. More in-depth research requires in future regarding comparison of role of oral iron supplementation in children suffering from ADHD with iron deficiency and in children suffering from ADHD without ID. Prevention is always better than cure and supply of fortified iron supplementation could bring down occurrence of ID in children suffering from ADHD.

Source of Funding and Support

The study was financially supported by intramural grant program [with Reference number: DMIMS (DU) R & D/2018–19/41] of Datta Meghe Institute of Medical Sciences (Deemed to be University), Sawangi, Wardha, Maharashtra, India in which patient's laboratory expenses were supported.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jan 25, 2020
- Manual Googling: Jul 31, 2020
- iThenticate Software: Sep 29, 2020 (3%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: As declared above
- Was informed consent obtained from the subjects involved in the study? Yes, (from parents)
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jan 24, 2020**
Date of Peer Review: **Feb 18, 2020**
Date of Acceptance: **Aug 06, 2020**
Date of Publishing: **Oct 01, 2020**