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Original Research Article

Iron status in children with attention - Deficit/hyperactivity disorder

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ABSTRACT

Background: Attention-deficit/hyperactivity disorder is one of the most common neurobehavioral disorders of childhood. The objectives of the study were to evaluate the status of iron stores in children with ADHD and to investigate a possible correlation between serum ferritin levels and severity of ADHD.
Materials and Methods: 60 children aged 3-12 years of age who were diagnosed to have ADHD as per the ICD 10 research Criteria for Hyperkinetic Disorder, were included in this study. After obtaining written informed consent from the child's guardian, severity score of ADHD was determined using Conner's Parent Rating Scale(CPRS), and blood investigations including Hb, PCV, blood indices, RDW, and serum ferritin were sent and results were statistically analysed
Results: Serum ferritin levels were between 15-30 ng/ml in 16 children (26.7%) and more than 30 in 44 children (73.3%). The CPRS severity scores were found to be higher among children belonging to the combined (72.7%) and hyperactive (59.4%) categories than among those belonging to the inattentive category (23.5%). The haemoglobin level was found to be low as per the WHO standards in only 3 out of the 60 children studied. All 3 children with Hb<11.5 belonged to the inattentive category. No significant correlation was found between serum ferritin levels and CPRS rating scores.
Conclusions: The iron status in children with ADHD in our study was not suggestive of iron deficiency. Iron deficiency probably occurs in a subset of children with ADHD and illy found. The study also did not find any significant correlation between serum ferritin levels and the severity scores of ADHD on CPRS.

1. Introduction

Attention-deficit/hyperactivity disorder is one of the most common neurobehavioral disorders of childhood. The prevalence rate of ADHD isestimated to be as high as 4% - 12% among school aged children in western studies[1] though there is no data available from India as to the actual prevalence rate. It is more prevalent in boys than girls.

ADHD is characterised by developmentally inappropriate and impairing levels of gross motor over activity, inattention, and impulsivity.[2] Children with ADHD tend to face several problems such as poor academic performance, interpersonal relationship problems, and low self-esteem. These children may also have associated behavioural, emotional, language or learning disorders.

ADHD usually starts during childhood and may persist through adolescence and adulthood in 30 – 50%. In adults it may lead on to adverse vocational outcomes, social dysfunction, and increased risk of antisocial behaviours including substance abuse and encounters with the law.

The aetiology of ADHD involves complex interactions of neuroanatomical and neurochemical systems. Dopaminergic mesocortical systems are thought to play a role in the etio-pathogenesis of ADHD.[3] Patients with ADHD have increased dopamine transporter binding potential and molecular genetic studies have also shown

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an association between ADHD and polymorphisms of dopamine receptor D4 gene, dopamine receptor D5 gene and dopamine transporter gene.[4]

Dopamine synthesis is dependent on the availability of iron as iron is a coenzyme for tyrosine hydroxylase, the rate limiting enzyme in dopamine synthesis. It is also postulated that iron deficiency affects dopamine levels in substantianigra and putamen.[5]

Several studies have investigated the possible involvement of iron as a cause of ADHD and the results have been mixed with some studies showing an increased. Most of these studies have employed serum ferritin as a marker as it is a reliable measure of peripheral iron stores and a low level can detect early iron deficiency that is sufficient to cause neurological and behavioural symptoms. However, ferritin is an acute phase reactant and its levels are increased in inflammatory diseases and subclinical infections and thereby no longer reflect the size of the body iron stores. Also, whether the serum ferritin levels correlate with brain iron is still a matter of debate.

As the exact aetiology of ADHD is still unknown and is thought to be due to an interaction between several genetic and environmental factors the current pharmacotherapy for ADHD is symptomatic rather than curative. Studies of iron status in ADHD have yielded mixed results showing both significant and non-significant association of ADHD symptoms with serum ferritin levels. There have not been many studies in this area from our part of the world. This study aimed to investigate the contribution of iron deficiency to the symptoms of ADHD in children which may help in the more effective treatment of the condition.

2. Materials and Methods

This descriptive study was conducted from March 2014 to September 2015 in Government TD Medical College Alappuzha. This study was approved by institutional research committee and the ethical committee. Children between 3-12 years of age attending the Pediatrics OPD and ward and the Psychiatry OPD diagnosed to have ADHD as per ICD 10 research criteria at Govt. T D Medical College, Alappuzha were included in the study. Children with malnutrition, IQ less than 85, with any acute severe illness in the past two weeks and children already on iron therapy for more than one week were excluded from the study.

Sample size was calculated to be 60 based on previous studies. A sample size of 69 was obtained.

After obtaining ethical clearance from the Institutional Ethical Committee and written informed consent from the child's guardian, a detailed history and a semi structured interview regarding the child's behavior was taken.

The clinical diagnosis and classification of ADHD was based on the ICD 10 Research Criteria. The severity of ADHD symptoms was evaluated using Conner's Parent Rating Scale.

Blood samples from the patient were collected for assessing Hb, PCV, blood indices (MCV, MCH, and MCHC), RDW, peripheral smear findings and serum ferritin levels using ELISA technique.

All the data obtained were entered in the proforma. Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) Version 16.0 software. All data were represented as frequency and percentages. Pearson Chi square test was used for qualitative variables. For all evaluations probability value of less than 0.05 was taken as significant.

3. Results

A total of 71 children were eligible for the study out of which 11 were excluded, 8 due to non-consent for performance of blood tests and 3 due to non-availability of the final reports.

Out of the total 60 children studied, majority (56) were boys, with only 4 girls included in the study.

Table 1: Gender distribution in study population.

Gender	Frequency	Percent
Male	56	93.3
Female	4	6.7
Total	60	100

32 children belonged to the predominantly hyperactive category of ADHD, 17 were predominantly inattentive and the remaining 11 belonged to the combined category.

Table 2: Distribution of ADHD sub-types in study population.

Type of ADHD	Frequency	Percent
Hyperactive	32	53.3
Inattentive	17	28.3
Combined	11	18.3
Total	60	100

While among the male cases, majority belonged to the predominantly hyperactive and combined types of ADHD, among the female subjects, although very few in number, majority belonged to the inattentive group.

Also it was seen that in the younger age group, most cases belonged to the predominantly hyperactive and combined categories while as the age of the cases advanced, the predominantly inattentive category also came to the fore.

The hemoglobin level was found to be low as per the WHO standards, in only 3 of the 60 children studied with 2 out of these 3 having a microcytic hypochromic picture in the peripheral smear.

Other blood indices were found to be on the lower side in majority. 55 children (91.7%) children had MCV values less than 81fl; 48 children (80%) had MCH values less than 28.6pg; and 36 children (60%) had MCHC values

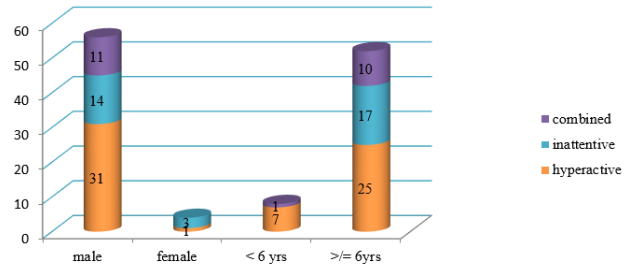

Fig. 1: Distribution of ADHD sub-types based on gender and age.

Table 3: Baseline characteristics of study population.

Parameters	Mean	±SD
Age (yrs)	8.18	2.19
Severity Score	39.55	7.61
Hb	12.74	0.77
PCV	36.89	2.19
MCV	76.97	2.68
MCH	26.52	2.10
MCHC	34.32	1.46
RDW	13.03	0.48
S. Ferritin	40.20	14.49

Table 4: Hemoglobin levels in study population.

Hemoglobin	Frequency	Percent
Low (< 11.5)	3	5
Normal	57	95
Total	60	100

less than 34.5g/dl., though none of the children had RDW more than 14.5% required for the classification of iron deficiency anemia, 51 of them (85%) had RDW between 12.5 and 14.5%.Serum ferritin levels were between 15 – 30ng/ml in 16 children (26.7%) and more than 30ng/ml in the remaining 44 children (73.3%).

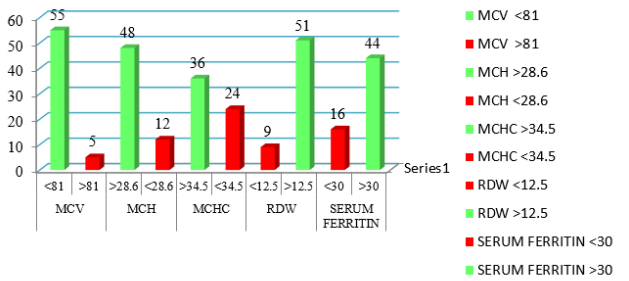

Fig. 2: Red blood indices, red cell distribution width (RDW) and serum ferritin levels in study population.

MCV= Mean corpuscular volume, MCH= Mean corpuscular hemoglobin, MCHC=Mean corpuscular hemoglobin concentration and RDW= Red cell Distribution Width Children with the combined (72.7%) and predominantly hyperactive (59.4%) types of ADHD scored higher on the CPRS while those with the predominantly inattentive (23.5%) type of ADHD had lower severity scores.

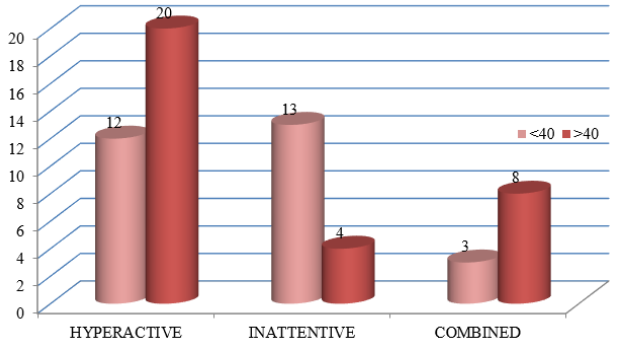

Fig. 3: Conner's parent rating scale scores in sub-types of ADHD

However, all 3 children with low Hb levels belonged to the less severe predominantly inattentive category.

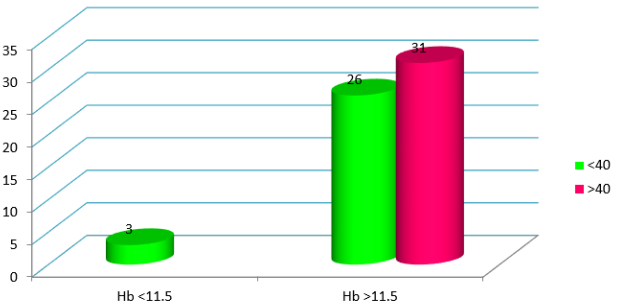

Fig. 4: Hemoglobin level in sub-types of ADHD

Using Pearson's Chi square test, no significant correlation was found between serum ferritin levels and CPRS severity scores.

Table 5: Correlation between serum ferritin levels and severity scores on CPRS

Serum Ferritin	Severity Score		Total
	Moderate (20-40)	Severe (>40)	
15 - 30	7	9	16
	24.10%	29.00%	26.70%
> 30	22	22	44
	75.90%	71.00%	73.30%
Total	29	31	60

Chi square- 0.184; p value > 0.05 (not significant).

In fact, on comparing the serum ferritin levels among 15 children with the highest and lowest scores on the CPRS, children with less severe form of ADHD was found to

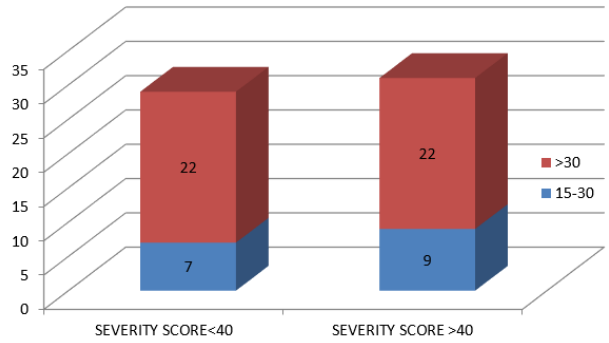

Fig. 5: Correlation between serum ferritin levels and severity scores on CPRS

have lower levels of ferritin (mean value of 32.86+/-4.56) compared to those scoring higher on the CPRS (mean value of 37.73 +/-4.96).

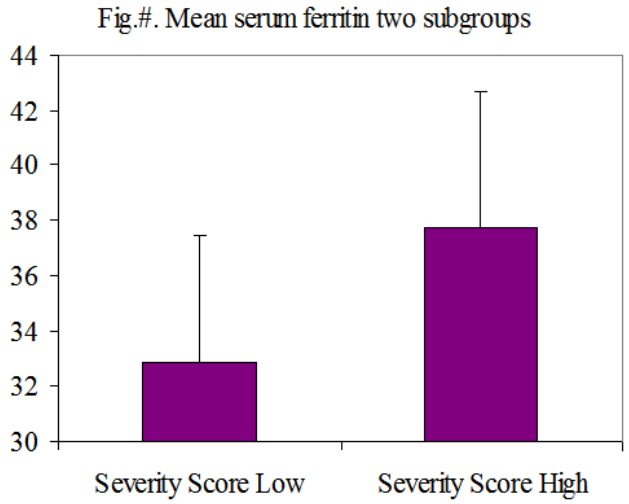

Fig. 6: Mean serum ferritin in children with maximal and minimal CPRS scores

The mean haematological parameters also did not show a significant difference on comparing children with scores <40 on the CPRS and those with score >40 on the CPRS.

4. Discussion

The purpose of our study was to find if iron deficiency was commonly seen in children with ADHD and also to investigate a possible correlation between the severity of iron deficiency as measured by serum ferritin levels and the severity of ADHD symptoms on the CPRS.

This study was a descriptive study done in children diagnosed to have ADHD as per the ICD 10 Research Criteria at the Pediatrics ward and OPD as well as the Psychiatry OPD at Government T. D. Medical College, Alappuzha.

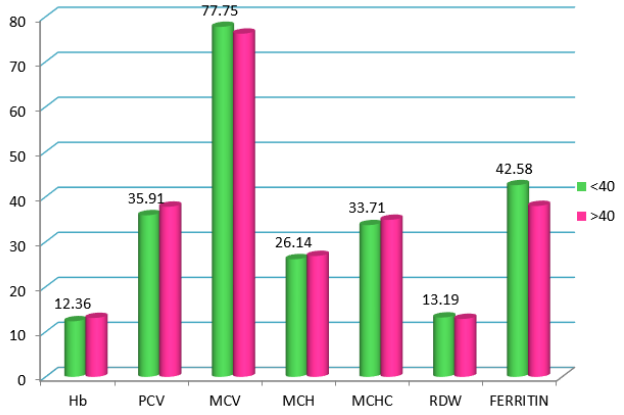

Fig. 7: Comparison of mean haematological parameters among children with high and low scores on CPRS.

The study included 60 patients, out of whom 56 were males and 4 were females in accordance with several previous studies that have shown a three- fold increased risk of ADHD in males than females. Boys are also found to be nine times more likely to be referred for evaluation and treatment. In this study, girls predominantly had attention problems compared to boys who were referred mainly for the hyperactive behaviour. Previous studies have also shown that girls tend to have more internalizing behaviours and often their difficulties are overlooked with the problem going unrecognised by parents and teachers.

Only 3 out of the 60 (i.e 5%) children studied had anemia as per the WHO criteria which was far less than the prevalence of anemia in Kerala as per the National Family Health Survey 3 (2011) of 43.5%. This could probably be because of the small sample size included in this study and also possibly because of the different methods used in the estimation of haemoglobin.

Though the red cell indices were low even in the absence of anemia in majority of the children included in our study, this was probably not significant as it has been proposed that this is a feature of erythropoiesis in children.

In our study, the CPRS severity scores were highest for children who belonged to the predominantly hyperactive and the combined types of ADHD. However, all the three children who had haemoglobin levels less than the WHO criteria for anemia belonged to the inattentive category with lower scores on the CPRS. These findings are in line with the results of the studies by Millichap et al[6] and Kiddie et al[7] where the mean serum ferritin levels in patients with ADHD were not significantly different from that of the national norms. Millichap et al also did not find any significant difference in clinical characteristics of children with low and high ferritin levels as in our study.

One of the major drawbacks of our study was that there was no control group and as such we were only able to

compare characteristics between children with the lowest and highest scores on CPRS as in the study by Millichap et al. However, there have been several studies with control groups which have also failed to show significant differences between the serum ferritin levels among children with ADHD and controls as well as any correlation between the symptom severity of ADHD and serum ferritin levels as in the study by Menegassi et al.[8] The largest controlled study by Donfrancesco et al[9] also did not find either a significant difference between serum ferritin levels in children with ADHD as compared to the controls or any significant difference between serum ferritin and ADHD subtypes or severity scores.

Several iron supplementation studies like those by Konofal et al[10] also did not find any significant improvement in severity scores of ADHD following iron supplementation. In the study in 2012 by Soto-Insuga et al,[11] iron deficiency was more frequently in the inattentive group as in our study. Iron supplementation was also found to be more effective in this category compared to the non-inattentive subtypes.

In contrast to the above studies , the only published study from India by Juneja et al[12] conducted at a tertiary hospital in New Delhi found that the serum ferritin levels were significantly lower in cases with ADHD as compared to controls. However there is a difference in the prevalence of anemia in the two states. The NFHS 3 shows the prevalence of anemia among pre-schoolers in New Delhi to be around 57% compared to 43.5% in Kerala. Also in this study, the ferritin levels showed a significant negative correlation between oppositional scores in both CPRS and CTRS. However, in this study, 44% cases had co-morbid Oppositional Defiant Disorder (ODD) so the results could be due to correlation between ODD and serum ferritin.

Most of the previous studies, where serum ferritin levels were found to be low among cases with ADHD, were conducted on a treatment naïve population. However, majority of the children in our study were already on medications like Atomoxetine which are known to suppress appetite and may consequently alter the serum ferritin levels. The weight loss associated with the use of Atomoxetine may also lead to increased serum ferritin levels due to the decreased iron utilisation. Also ours was a heterogeneous population including children with seizure disorder; specific learning disorders etc and the extent to which these factors contribute to anemia were not taken into account. This heterogeneity may have contributed to the discordance in results. Several lines of research have shown that ADHD is highly heterogeneous in terms of etio-patho-physiology, hence it is reasonable to conceive that iron deficiency characterises a subsample of ADHD children rather than all children with ADHD. Work by Konofal et al[10] and by Oner's group[13] suggest that children with sleep disorders, particularly restless leg syndrome, may be a subgroup at risk of iron deficiency and severe ADHD symptoms.

Whether serum ferritin levels correlate with the brain iron levels is also unclear. Preliminary recent studies have suggested that there may be a deficiency of brain iron in individuals with ADHD. The study by Cortese et al[14] found the serum ferritin levels in children with ADHD to be lower than that in controls. They also found that children with ADHD showed significantly lower estimated brain iron in right and left thalami compared to healthy controls. However, serum ferritin and brain iron values on T2 weighted images did not correlate significantly in most regions. This calls for more studies comparing the brain iron levels in children with ADHD which is crucial in better establishing a link between iron deficiency and ADHD symptoms. A reduced amount of peripheral iron may have an effect on central iron levels. However a normal ferritin level does not necessarily reflect normal brain iron. For example, a dysfunction in the blood brain barrier can lead to decreased iron entry into the brain and therefore reduced brain iron levels in the presence of normal peripheral iron. Recently, a study by Connor et al[15] reported a deficit in the entry of iron in the brain in patients with RLS. Patients with RLS appear to have reduced brain iron levels which could be insufficient for appropriate brain functioning even with normal peripheral iron levels. Cortese et al[14] speculated that dysfunction in the blood brain barrier or iron transport mechanisms in children with ADHD with or without RLS may be responsible for a possible mismatch between peripheral and central iron levels. As such, it is possible that individuals with ADHD have a brain iron deficiency in the presence of normal or subnormal serum ferritin levels.

5. Conclusion

Our study did not find an increased prevalence of anemia in chidren with ADHD. It also did not find any significant correlation between the severity of ADHD symptoms on the CPRS and the serum ferritin levels. The results from this preliminary study suggest that iron deficiency may not be universally present in all children with ADHD, rather it may just represent a subset of children with ADHD and other comorbidities. Clinicians must further evaluate other causes of anemia before prescribing iron supplements in children with ADHD even if the haemoglobin values are low. There is also a need for more studies looking into the correlation between serum ferritin levels and brain iron levels as it is the brain iron that is expected to impact neuronal functions and myelination of white matter thus affecting ADHD symptoms. Therefore we can conclude that besides an assessment of peripheral iron markers, an estimation of brain iron levels is crucial to establish a possible role of iron deficiency in the pathophysiology of ADHD.

Table 6: Prior studies done in this area

Study (year)	ADHD	Controls	Serum Ferritin (ng/ml)	Key Findings
	n(m)age(SD/ range; yrs)	n(m) age(SD/ range; yrs)	mean(SD)	
Millichap et al(2006)	68(54) 5 - 16	- -	39.9(40.6)	Mean SF comparable with population norms;clinical characteristics not significantly different in those with SF>20 and SF<20
Menegassi et al(2010)	41(31) 8.8(2.4)	21(15) 8.9(2.7)	R^x59.3(21); naïve 54.2(17.2)	No significant difference in mean SF between ADHD and comparisons
Donfrancesco et al(2012)	101(92) 8.9(2.6)	93(82) 9.1(3.0)	ADHD 33(17.8);control 33.14(18.7)	No significant association between SF levels and ADHD types,IQ,ADHD severity

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7. Conflict of Interest

The authors declare no relevant conflicts of interest.

8. Source of Funding

None.

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