SHORT COMMUNICATION

Iron Deficiency in Indian Children with Attention Deficit Hyperactivity Disorder

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A case control study was conducted at the Child Development and Early Intervention Clinic to determine the body iron status of children with ADHD, and study the correlation between the body iron status and ADHD symptoms. Serum ferritin was measured in newly diagnosed cases with ADHD and compared with that of controls. Correlation was studied between serum ferritin levels and the severity of ADHD symptoms as determined by Conners' Rating Scale. Serum ferritin was found to be significantly lower in children with ADHD (6.04 ± 3.85 ng/mL) as compared to controls (48.96 ± 41.64 ng/mL, *P* value<0.001). There was a significant negative correlation between serum ferritin levels and oppositional subscore on Conners' Rating Scale.

Key words: *Attention Deficit Hyperactivity Disorder, Children, Ferritin, India, Iron*.

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Attention deficit hyperactivity disorder (ADHD) is amongst the most common neurobehavioral disorders in children, with prevalence rate as high as 4%-12% in school-aged children(1). It is characterized by three core symptoms of inattention, hyperactivity and impulsivity(2). Multiple theories of ADHD have been proposed, but the dopamine deficit theory is the most widely accepted. Brain imaging and functional studies have shown abnormalities in the dopamine modulated frontal-striatal circuits(3). Molecular genetic studies have also shown an association between ADHD and polymorphisms of dopamine receptor D4 gene, dopamine receptor D5 gene and dopamine transporter gene(3,4). Dopamine synthesis is dependent on availability of iron, as it is a coenzyme of tyrosine hydroxylase, which converts tyrosine to L-dopa, which is then decarboxylated to dopamine(5).

Role of iron has also been extensively studied in Restless leg syndrome (RLS), a condition related to ADHD. Iron deficiency has been associated with secondary RLS and aggravates of idiopathic RLS(6,7). It is postulated that iron deficiency affects dopamine levels in substantia niagra and putamen(8). Iron deficiency is also associated with a number of other neurologic disorders including development delay, stroke, pseudotumor cerebri, breath-holding episodes and cranial nerve palsies(9). Recently, its possible involvement as a contributing cause of ADHD has also been reported from some developed countries(10-15). Serum ferritin is a reliable measure of iron stores in body tissues, including brain, and low level can detect an early iron deficiency sufficient to cause neurological or behavioral symptoms. This study was planned to investigate the contribution of iron deficiency to the ADHD symptoms in the Indian setting.

METHODS

A case control study was conducted in Child Development and Early Intervention Clinic (CDEIC) in the Department of Pediatrics, of a tertiary care hospital in New Delhi, India in the year 2007. All 6-14 years old children who were newly diagnosed as ADHD in the clinic as per DSM IV TR criteria and with hemoglobin of >10 g/dl were included in the study. To confirm the presence of symptoms in two settings, only children with both Conners' Parents Rating Scale (CPRS) and Conners' Teachers Rating Scale (CTRS) T-scores of ≥65 were included.

Age and sex matched children without ADHD or mental retardation was taken as controls. Children who were already on iron therapy for more than one week were excluded from the study. Those with IQ less than 85, any chronic illness, or any acute severe illness in last two week were also excluded.

After taking consent from the parents, detailed history and a semi-structured interview regarding child's development and behavior was taken, followed by detailed examination. Intelligence testing was done by Indian adaptation of the Wechsler Intelligence Scale for children.

The diagnosis and classification of ADHD was made according to DSM-IV-TR criteria. The severity of ADHD symptoms was then evaluated using both CPRS and CTRS, including the hyperactivity, cognitive, and oppositional subscales. Childhood Autism Rating Scale was also administered to all cases to rule out autism.

Fasting blood sample was taken for measuring serum ferritin level using ELISA and hemoglobin levels. All children with ADHD were started on behavior modification therapy. Those not responding adequately to these interventions were offered adjunctive methylpheni-date therapy. Children with iron deficiency were also given iron supplements.

The ethical committee of our hospital approved the study. Statistical analysis was carried out using SPSS software. Pearson test was used for correlations between symptom severity and serum ferritin levels.

RESULTS

37 children were eligible for the study, out of which 12 were excluded because of non-availability of CTRS in 10 and refusal to give fasting blood sample for serum ferritin in 2 cases. The final study group comprised of 25 children, 21 (84%) males and 4 (16%) females. 25 age and sex matched children without ADHD or mental retardation were taken as controls (***Table* I**).

Out of 25 cases diagnosed as ADHD, 23 (92%) were of combined type and 2 (8%) were of hyperactive-impulsive type. None of them was of purely inattentive type. The severity of ADHD symptoms evaluated using CPRS and CTRS in various subscales is shown in ***Table* II.** Oppositional defiant disorder (ODD) was present in 11 cases (44%) and conduct disorder was present in 2 cases (8%). Family history suggestive of ADHD was present in 11 cases (44%). 44% of cases and 84% of controls were from lower socioeconomic class (P=0.003).

Serum ferritin was found to be low (<12 ng/mL) in 23 (92%) cases with ADHD whereas none of the controls had low values. Mean (± SD) serum ferritin levels in cases (6.04±3.85 ng/mL) were significantly lower than that of controls (48.96 ± 41.64 ng/mL) (P <0.001). The range of serum ferritin in cases was 0.01-14.0 ng/mL and in controls was 18-170 ng/mL. The CPRS oppositional scores were significantly correlated with serum ferritin level; ADHD children with lower ferritin levels had higher scores, indicating more severe problems (Pearson

TABLE I CHARACTERISTICS IN THE STUDY POPULATION

	Cases mean± SD	Controls mean± SD	*P* value value
Age, yrs	8.44±1.68	7.96±1.46	0.286
Weight, kg	26.00±7.34	24.62±8.10	0.530
Height, cm	132.88±9.79	128.60±10.06	0.133
School grade level	2.96±1.09	3.25±0.96	0.323
IQ	104.2± 8.1	100.3± 5.7	0.152
Hb, gm%	11.97± 0.62	11.93± 0.70	0.849
Hematocrit, %	35.7±1.95	35.4±2.08	0.625

correlation coefficient, r=–0.405, *P*=0.022). The CTRS oppositional scores were also significantly correlated with serum ferritin level (r = –0.484, *P*=0.014).

No significant correlation was found between ferritin levels and CPRS inattentive scores or CTRS inattentive scores. Similarly, there was no significant correlation of ferritin levels with CPRS or CTRS hyperactivity scores. There was no correlation between serum ferritin levels of controls and T-scores of controls for any of the symptoms.

DISCUSSION

We found that the level of serum ferritin was significantly lower in cases with ADHD as compared to controls. We also found that the ferritin levels showed a significant negative correlation with oppositional scores in both Conners' parent and teacher rating scales. There was a negative correlation between ferritin levels and T-scores for both hyperactivity and inattentiveness but this did not reach statistical significance. These findings suggest that iron deficiency may explain some symptoms of ADHD.

However there were some limitations in this study. The number of cases included was small, partly due to the strict inclusion criteria of the study. Also in our region, only severe cases seek medical advice for behavioral/school related problems and most with mild to moderate problems are not brought to medical attention. Thus this data may represent only severe cases with ADHD. Moreover, in this study, 44% of cases had co-morbid ODD and we found significant negative correlation of serum ferritin with only oppositional scores. The results obtained in this study could be due to correlation between ODD and serum ferritin.

In a former similar study, mean serum ferritin levels were also found to be significantly lower in the children with ADHD (23±13 ng/mL) as compared to controls (44±22 ng/mL). The serum ferritin levels correlated with ADHD symptoms severity measured with CPRS. Serum ferritin levels also correlated with the cognitive subscore and tended toward a correlation with the hyperactivity subscore but did not correlate with the oppositional subscore(10). In another study on 52 ADHD children, lower ferritin levels were associated with higher hyperactivity scores on CPRS(11). However, in contrast to these two studies, we found that serum ferritin levels did not correlate significantly with hyperactivity or cognitive sub-score. This could be because there was not much variation in the serum ferritin levels in our cases, as all patients with ADHD had serum ferritin below 15ng/mL. It could also be because of small sample size of our study.

In a previous large study on subjects with ADHD, CPRS and CTRS total scores were negatively correlated with serum ferritin with more prominent negative correlation in the comorbid ADHD subjects. This study concluded that presence of comorbid conditions might increase the effect of lower iron stores on behavioral measures(12). ADHD children with lower serum ferritin levels were also shown to have higher scores on Sleep Disturbance Scale for Children(14).

In contrast to the results of above studies, in the study by Millichap, *et al*.(15), the mean serum ferritin level in patients with ADHD was not different from that of controls. Also in this study there was no difference in the clinical characteristics of patients with lowest and highest serum ferritin levels. However, the population enrolled in this study was heterogeneous with seizure disorders, neurological deficits and learning difficulties. They

TABLE II DISTRIBUTION OF T- SCORES OF ADHD PATIENTS

	Oppositional		Inattentive		Hyperactive	
	Parent	Teacher	Parent	Teacher	Parent	Teacher
Minimum	54	52	52	49	64	64
Maximum	90	90	90	86	90	90
Mean	68.64	71.04	70.38	65.96	78.92	75.24

WHAT THIS STUDY ADDS?

- In similar settings, iron deficiency may contribute to the symptoms of attention deficit hyperactivity disorder.

did not have any controls in their study but have compared their results with National U.S. data. Failure to find any differences in this study may only signify that low iron levels may not be a universal finding in children with ADHD but needs to be addressed in those with deficiency.

Thus, from the results of this preliminary study, we conclude that iron deficiency might contribute to the symptoms of ADHD and iron deficient children may have more severe manifestations. Since iron deficiency is quiet common in India and other low-income countries, its contribution to symptoms of ADHD and other behavioral problems needs to be further assessed by larger population based studies, including the response to iron therapy.

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REFERENCES

1. Brown RT, Freeman WS, Perrin JM, Stein MT, Amler RW, Feldman HM, *et al*. Prevalence and assessment of attention-deficit/hyperactivity disorder in primary care setting. Pediatrics 2001; 107: e43.
2. Malhi P, Singhi P. Diagnosis and management of children with attention deficit hyperactivity disorder. Indian J Pediatr 2001; 68: 547-555.
3. Swanson JM, Kinsbourne M, Nigg J, Lanphear B, Stefanatos GA, Volkow N, *et al*. Etiologic subtypes of attention-deficit/hyperactivity disorder: brain imaging, molecular genetic and environmental factors and the dopamine hypothesis. Neuropsychol Rev 2007; 17: 39-59.
4. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, *et al*. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry. 2005; 57: 1313-1323.
5. Sachdev P. The neuropsychiatry of brain iron. J Neuropsychiatry Clin Neurosci 1993; 5: 18-29.
6. Bayard M, Avonda T, Wadzinski J. Restless legs syndrome. Am Fam Physician 2008; 78: 235-240.
7. Frauscher B, Gschliesser V, Brandauer E, El-Demerdash E, Kaneider M, Rücker L, *et al*. The severity range of restless legs syndrome (RLS) and augmentation in a prospective patient cohort: association with ferritin levels. Sleep Med 2009; 10: 611-615.
8. Connor JR. Pathophysiology of Restless legs syndrome: evidence for iron involvement. Curr Neurol Neurosci Rep 2008; 8: 162-166.
9. Yager JY, Hartfield DS. Neurologic manifestations of iron deficiency in childhood. Pediatr Neurol 2002; 27: 85-92.
10. Konofal E, Lecendreux M, Arnulf I, Mouren M-C. Iron deficiency in children with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 2004; 158: 1113-1115.
11. Oner O, Alkar OY, Oner P. Relation of ferritin levels with symptom ratings and cognitive performance in children with attention deficit-hyperactivity disorder. Pediatr Int 2008; 50: 40-44.
12. Oner P, Oner O. Relationship of ferritin to symptom ratings children with attention deficit hyperactivity disorder: effect of comorbidity. Child Psychiatry Hum Dev 2008; 39: 323-330.
13. Konofal E, Lecendreux M, Deron J, Marchand M, Cortese S, Zaïm M, *et al*. Effects of iron supplementation on attention deficit hyperactivity disorder in children. Pediatr Neurol 2008; 38: 20-26.
14. Cortese S, Konofal E, Dalla Bernardina B, Lecendreux M. Sleep disturbances and iron deficiency in children with ADHD. Eur Child Adolesc Psychiatry 2009; 18: 393-399.
15. Millichap JG, Yee MM, Davidson SI. Serum ferritin in children with attention deficit hyperactivity disorder. Pediatr Neurol 2006; 34: 200-203.