A study on association of iron deficiency with attention deficit hyperactivity disorder in a tertiary care center

Kamirul Islam, Soutrik Seth, Suman Saha, Atanu Roy, Rajib Das, Asok Kumar Datta
Department of Pediatrics, Burdwan Medical College, Burdwan, West Bengal, India

INTRODUCTION

Most prevalent nutrient deficiency among children and adolescents is iron deficiency according to the estimation of the WHO.[1] Iron deficiency is detected sometimes in asymptomatic individuals insidiously. However, it is generally manifested by pallor, shortness of breath, and lethargy. Iron is an important component of several metalloproteins such as hemoglobin (Hb), myoglobin, and many enzymes having role in cellular metabolism. Iron deficiency significantly alters the intracellular and extracellular concentration of different neurotransmitters such as dopamine, serotonin, and norepinephrine in different areas of the brain, predominantly in locus ceruleus and basal ganglia (mainly in substantia nigra and putamen).[2] Iron deficiency also alters the expression of transporters of different neurotransmitters. There is documented evidence in literature that iron deficiency is associated with cognitive impairment and may be associated with many neuropsychiatric manifestations such as attention deficit hyperactivity disorder (ADHD).

Background: Iron is important for brain development and cognitive function. Iron deficiency may cause alteration of neurotransmitters and may be manifested by different central nervous system disorders including attention deficit hyperactivity disorder (ADHD).

Aims: As studies are scarce in the Indian context, we had undertaken this study to find out the association between iron deficiency and ADHD.

Settings and Design: Hospital-based cross-sectional study.

Materials and Methods: Hematological parameters indicating iron status (hemoglobin [Hb], ferritin, iron, total iron binding capacity [TIBC], mean corpuscular volume [MCV], and mean corpuscular Hb [MCH]) were measured among 119 ADHD patients selected by complete enumeration method and 119 controls.

Statistical Analysis: Shapiro–Wilk test, Mann–Whitney U-test, Spearman’s correlation, and binary logistic regression were used. P < 0.01 was taken as statistically significant.

Results: Hb, iron, ferritin, MCV, and MCH were lower among cases and negatively correlated to ADHD, while reverse is true for TIBC and ADHD. Iron deficiency anemia makes one 3.82 times more prone for ADHD.

Conclusion: Iron deficiency was associated with ADHD.

Key words: Attention deficit hyperactivity disorder, children, ferritin, iron deficiency, total iron binding capacity

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Islam K, Seth S, Saha S, Roy A, Das R, Datta AK. A study on association of iron deficiency with attention deficit hyperactivity disorder in a tertiary care center. Indian J Psychiatry 2018;60:131-4.
hyperactivity disorder (ADHD), autism spectrum disorder, anxiety disorder, and bipolar mood disorders. Among them, ADHD is most common in school-going children having a prevalence of 4%–7% characterized by three cardinal features—attention deficit, impulsivity, and hyperactivity. Beside some genetic causes (polymorphism of dopamine receptor genes (D4 and D5) and dopamine transporters), it is also assumed that ADHD is caused by alteration of different neurotransmitters level. Iron act as cofactor of tyrosine hydroxylase, an enzyme of neurotransmitter synthesis. Hence, iron deficiency may cause alteration dopamine levels in substantia nigra and putamen. Iron deficiency may also cause restless leg syndrome, which in turn may lead to ADHD. ADHD is a treatable cause of many future problems such as educational difficulty, social exclusion, school dropout, and criminality.

Multiple studies from different parts of the world reported that there is an association between iron deficiency and ADHD. In India, one study was conducted where serum ferritin level of children with ADHD was estimated. Hence, we had undertaken this study to find out the association between iron deficiency (by measuring hematological variables indicating iron status) and ADHD.

MATERIALS AND METHODS

A hospital-based (outpatient based) cross-sectional study was conducted among the children diagnosed with ADHD in between February 2015 and March 2017 in the pediatric and psychiatry outpatient clinic of Burdwan Medical College, Burdwan, after obtaining ethical clearance from the Institution Ethics Committee. One hundred and nineteen cases were selected by complete enumeration method at the time of diagnosis before starting any kind of treatment for ADHD (taking prevalence of ADHD as 5%, confidence interval as 95%, and population size as infinite, sample size required to obtain a statistically significant result is 73). All children and adolescents (upper age limit - 19 years) who were diagnosed as ADHD were included in the study. Children who were on oral iron supplements, whose parents did not will to participate in the study and who were seriously ill, were excluded from the study (11 children were excluded from the study, two for not giving consent, seven were on oral iron supplement and blood samples of two children were lost during transport to the laboratory). Age- and sex-matched controls were selected from patients going to laboratory for routine blood tests for elective surgery which are not supposed to alter parameters indicating iron status of children/adolescents. Before enrolment of controls, ADHD was excluded among them. Some parameters indicating iron status such as Hb, serum iron, serum ferritin, total iron binding capacity (TIBC), mean corpuscular volume (MCV), and mean corpuscular Hb concentration (MCHC) were checked for both cases and controls. Blood samples were collected on the next working day after diagnosis, in fasting state. For quality control, all the tests were done in the same laboratory of our college. For estimation of serum iron and TIBC, Erba Chem 5+ V2 was used (Ferrozinc method). For assessment of serum ferritin, Tosho AIA 360 was used. Each report was double-checked by two different laboratory technicians. They were not informed about the purpose of the study. The same analyzers were used to perform the tests.

ADHD was diagnosed in children and adolescents according to Diagnostic and Statistical Manual of Mental Disorders 5th Edition criteria. Its severity was assessed by Conner’s rating scale, for teachers and parents (Conners’ Teacher Rating Scale and Conners’ Parent Rating Scale, respectively).

Collected data were entered into Microsoft Excel Worksheet. Categorical data were coded (ADHD: Yes-1/no-0). Using Shapiro-Wilk test (as sample size is <2000), we found that data were skewed. Hence, median and interquartile range were calculated for each continuous variable. A nonparametric test (Mann-Whitney U-test) was used for checking the association between different variables in contingency tables. Significantly associated variables in the table were further considered for Spearman’s rank-order correlation to find out the strength and association of the relationship which is measured by Spearman’s coefficient (r). Finally, a binary logistic regression model (forward conditional method) was created taking ADHD as dependent/outcome variable. Adjusted odds ratio (OR) was determined with 95% confidence interval. P < 0.01 was considered as statistically significant. All the statistical analysis was done to by SPSS software version 20.0 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA).

RESULTS

Mean age of the study population was 11.0 ± 3.7 years and 70.6% of them were male. 64.1% of them belonged to Hindu religion. Majority (59.7%) of the ADHD patients belonged to 11–15 years of age group. There was no significant difference between the cases and controls in their age, sex, and socioeconomic status (P > 0.01) [Table 1].

Median level of Hb (8.3, 1.3 vs. 12.9, 2.0 mg/dl), serum ferritin (35.2, 4.7 vs. 43.8, 6.1 ng/ml), serum iron (43.8, 6.1 vs. 92.5, 7.8 µg/dl), MCV (92.5, 7.8 vs. 93.2, 5.9 fl), and MCHC (93.2, 5.9 vs. 30.8, 4.5 g/dl) level were significantly higher in control group. On the other hand, median TIBC level was significantly higher among ADHD patients (350.9, 10.4 µg/dl) than controls (334.1, 5.2 µg/dl) [Table 2]. Hence, there was a relative iron deficiency state among the patients of ADHD. About 22% (26 out of 119) of the patients of ADHD were suffering from iron deficiency anemia (IDA) while only 7% (8 out of 119) of controls were suffering from IDA (χ² = 9.44, P < 0.01).
ADHD is significantly and negatively correlated with Hb (\( r = -0.86 \)), serum ferritin (\( r = -0.83 \)), serum iron (\( r = -0.80 \)), MCV (\( r = -0.74 \)), and MCHC (\( r = -0.17 \)) signifying that an iron deficiency state is a risk factor of ADHD. While ADHD was significantly and positively correlated to serum TIBC (\( r = 0.86 \)) [Table 3]. Correlation coefficient (\( r \)) between IDA and ADHD is 0.76 (\( P < 0.01 \)). We did not find any significant correlation between severity of ADHD (measured by Conner’s rating scale) and hematological indicators of iron deficiency.

In our model, we found that higher level of Hb, serum ferritin, serum iron, MCV, and MCHC were protective for ADHD having an adjusted OR of 0.37 (95% confidence interval [CI] =0.27–0.46), 0.47 (95% CI = 0.44–0.50), 0.46 (95% CI = 0.42–0.50), 0.58 (95% CI = 0.40–0.77), and 0.99 (95% CI = 0.001–), respectively. Increased serum TIBC level and IDA were found to be risk factors of ADHD and their adjusted OR respectively were 1.73 (95% CI = 1.21–2.23) and 3.82 (95% CI = 3.30–4.34). All these ORs were statistically significant (\( P < 0.01 \)) except for MCH.

Serum ferritin, serum iron, and Hb can explain 46.7%–61.2% variance of ADHD. Serum ferritin alone can explain 34.1%–46.7% variance of ADHD. 32.0%–44.2% variance of the dependent variable can be explained by IDA alone. Overall, our model can correctly predict 44% of the outcome variable. Although MCH had a significant correlation with the dependent variable in the correlation matrix, it became insignificant in our regression model.

### DISCUSSION

We found that serum ferritin level was significantly lower among ADHD patients. This finding is consistent with multiple previous studies. Konofal et al.,[12] Calarge et al.,[13] and Juneja et al.,[14] and many other studies[3,4,7] reported an association between iron deficiency and ADHD. Although serum ferritin level of cases (34.9 ± 2.8 ng/ml) in our study is slightly higher than that found by Konofal et al.[12] (23 ± 13 ng/ml). In a previous Indian study, Juneja et al.[13] also noted a lower level of serum ferritin among ADHD patients (6.04 ± 3.85 vs. 48.96 ± 41.64 ng/ml). Ferritin level of their cases was also lower than ours, but standard deviation found by them was also quite high signifying a wider range of ferritin level among patients. Calarge et al.,[13] Sever et al.,[15] and Kwon et al.[16] also reported similar results from different parts of the world. Konofal et al.[12] and Calarge et al.[13] also reported a weak but significant inverse correlation between ADHD severity and serum ferritin level. However, we did not find any correlation between ADHD severity and serum ferritin level, which is similar to the findings of Juneja et al.[14] Juneja et al.[14] also calculated a correlation coefficient of –0.48 between serum ferritin level and ADHD, which is slightly lower than our finding.

In contrast to the above-mentioned studies, Millichap et al.[17] did not find any significant lowering of serum ferritin among ADHD children. However, he did not have controls in his study. Instead, he compared his findings with national database. Their findings may suggest that iron deficiency is not a universal finding for ADHD.

Besides this, we also found that mean Hb, serum iron, MCV, and MCH were lower among ADHD patients while the reverse is true for TIBC. Similar findings were also noted by Kwon et al.[16] among Korean children. However, the difference is significant for all parameters in our study, on
the other hand, Kwon et al.\textsuperscript{14} found significant difference only for TIBC, MCV, and MCH. But Konofal et al.\textsuperscript{12} did not find any in serum ferritin iron and hematocrit levels of cases and controls. However, contrary to the findings of Konofal et al.\textsuperscript{12}, Bener et al.\textsuperscript{18} from Qatar reported an increased level of serum iron and Hb among control than ADHD patients. We also noticed the same. Contrast to the observation of Kwon et al.\textsuperscript{14}, we found a stronger correlation of ADHD with Hb, ferritin, TIBC, MCV, MCH, and IDA. We found that who have IDA were 3.82 times more prone to develop ADHD, which is slightly higher to the findings of Chen et al., who found an OR of 1.51 (95% CI: 1.12–2.04). In our study, iron deficiency can explain 32.0%–44.2% variability of ADHD, whereas Konofal et al.\textsuperscript{12} can explain 30%.

Although our study had an adequate sample size, it has some limitations. Different studies had reported the different prevalence of ADHD, depending on which sample size may also vary. Hence, our sample size may become inadequate if the prevalence is more. In rural India (where our hospital is situated), there is still stigma about psychiatric disorders, and only the parents of severely ill children/adolescents seek medical advice. Hence, our study may not represent the status of all cases present in the community. Different types of ADHD are not addressed in this study. Sometimes, ADHD may be caused by restless leg syndrome due to iron deficiency.\textsuperscript{9,10} Although the incidence of such ADHD is less and the ultimate cause is iron deficiency, sleep status of the cases should be assessed which is beyond our reach. Although our findings are similar to that of multiple studies from different parts of India and other countries, multi-centric/longitudinal studies should be conducted before generalization of these findings. However, in many settings, different investigators noted that iron deficiency is associated with not only ADHD but also with different others central nervous system dysfunction. Hence, iron prophylaxis may be recommended.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. World Health Organization. Iron Deficiency Anaemia: Assessment, Prevention and Control. A Guide for Programme Managers. Geneva: World Health Organization; 2001.
2. Sachdev P. The neuropsychiatry of brain iron. J Neuropsychiatry Clin Neurosci 1993;5:18-29.
3. Yager JY, Hartfield DS. Neurologic manifestations of iron deficiency in childhood. Pediatr Neurol 2002;27:85-92.
4. Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, Chang WH, et al. Association between psychiatric disorders and iron deficiency anemia among children and adolescents: A nationwide population-based study. BMC Psychiatry 2013;13:161.
5. Brown RT, Freeman WS, Perrin JM, Stein MT, Amerl RW, Feldman HM, et al. Prevalence and assessment of attention-deficit/hyperactivity disorder in primary care settings. Pediatrics 2001;107:E43.
6. Eaves LJ, Silberg JL, Meyer JM, Maes HH, Simonoff E, Pickles A, et al. Genetics and developmental psychopathology: 2. The main effects of genes and environment on behavioral problems in the Virginia twin study of adolescent behavioral development. J Child Psychol Psychiatry 1997;38:959-60.
7. Lahat E, Heyman E, Livne A, Goldman M, Berkovitch M, Zachor D, et al. Iron deficiency in children with attention deficit hyperactivity disorder. Isr Med Assoc J 2011;13:530-3.
8. 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.
9. Castano-De la Mota C, Moreno-Acero N, Losada-Del Pozo R, Soto-Insuga V, Perez-Villena A, Rodrigue-Fernandez C, et al. Restless legs syndrome in patients diagnosed with attention deficit hyperactivity disorder. Rev Neurol 2017;64:299-304.
10. Miano S, Esposito M, Foderaro G, Ramelli GP, Pezzoli V, Manconi M, et al. Sleep-related disorders in children with attention-deficit-hyperactivity disorder: Preliminary results of a full sleep assessment study. CNS Neurosci Ther 2016;22:906-14.
11. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). St. Louis, MI, USA: APA; 2013.
12. Konofal E, Lecendreux M, Arnulf I, Mouren MC. Iron deficiency in children with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 2004;158:1113-5.
13. Calarge C, Farmer C, DiSilvestro R, Arnold LE. Serum ferritin and amphetamine response in youth with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol 2010;20:495-502.
14. Juneja M, Jain R, Singh V, Malik V. Iron deficiency in Indian children with attention deficit hyperactivity disorder. Indian Pediatr 2010;47:955-8.
15. Sever Y, Ashkenazi A, Tyrano S, Weizman A. Iron treatment in children with attention deficit hyperactivity disorder. A preliminary report. Neuropsychobiology 1997;35:178-90.
16. Kwon HJ, Lim MH, Ha M, Kim EJ, Yoo SJ, Kim JW, et al. Transferf in Korean children with attention deficit hyperactivity disorder. Psychiatry Investig 2011;8:366-71.
17. Millichap JG, Yee MM, Davidson SI. Serum ferritin in children with attention-deficit hyperactivity disorder. Pediatr Neurol 2006;34:200-3.
18. Bener A, Kamal M, Bener H, Bhugra D. Higher prevalence of iron deficiency as strong predictor of attention deficit hyperactivity disorder in children. Ann Med Health Sci Res 2014;4:S291-7.