Original Article

Higher Prevalence of Iron Deficiency as Strong Predictor of Attention Deficit Hyperactivity Disorder in Children

Bener A[1,2,3], Kamal M[4,5], Bener HZ[1,4], Bhugra D[6]

[1]Departments of Medical Statistics and Epidemiology, and [4]Pediatrics, Hamad Medical Corporation, [2]Departments of Public Health, and [5]Pediatrics, Weill Cornell Medical College, Doha, Qatar, [3]Department Evidence for Population Health Unit, School of Epidemiology and Health Sciences, The University of Manchester, Manchester, [6]Department of Psychiatry, Section of Cultural Psychiatry, Institute of Psychiatry, King's College London, London, UK

Address for correspondence:
Prof. Abdulbari Bener,
Department of Medical Statistics and Epidemiology, Hamad Medical Corporation, PO Box 3050,
Doha, Qatar.
E-mail: abb2007@qatar-med.cornell.edu

Abstract

Background: It has been reported that ferritin and iron deficiency may be related to the path physiology of attention deficit hyperactivity disorder (ADHD). **Aim:** The aim of this study was to determine the association between iron deficiency and ADHD and the impact and role of iron deficiency on the development of ADHD in children. **Subjects and Methods:** The study based on the case-control study age- and sex-matched control and conducted at the School Health and Primary Healthcare Clinics, Qatar. A total of 630 children with ADHD aged 5-18 and 630 controls aged 5-18 years old. Sociodemographic and clinical data were collected, including physician diagnosis. The health status of the subjects was assessed by ascertaining clinical presentations and symptoms, family history, body mass index (BMI), iron deficiency, ferritin, serum 25-hydroxyvitamin D, calcium, magnesium, and phosphorus levels. Descriptive, univariate, and multivariate statistical analysis were performed. **Results:** Mean age (standard deviation [SD] in years) for ADHD and control children were 11.54 (3.83) versus 11.50 (3.62). There were statistically significant differences between ADHD versus control children for vitamin D [16.81 (7.84) vs. 22.18 (9.00) ng/ml], serum iron [82.11 (13.61) vs. 85.60 (12.47) ng/ml], ferritin [36.26 (5.93) vs. 38.19 (5.61) ng/ml], hemoglobin [12.02 (2.13) vs. 12.89 (2.02) g/dL], magnesium [0.82 (0.08) vs. 0.88 (0.06) mmol/L], serum calcium level [2.35 (0.12) vs. 2.39 (0.14) mmol/L], and phosphorous [1.47 (0.30) vs. 1.54 (0.26) mmol/L]. Of total 630 of ADHD children, 116 (18.4%) had severe vitamin D deficiency (<10 ng/ml). Multivariate logistic regression analysis revealed that serum vitamin D level, serum iron, ferritin, serum calcium level, physical activity, nervous behavior, consanguinity, BMI, and child order were considered as the main factors associated with the ADHD after adjusting for age, gender, and other variables. **Conclusion:** The study indicates that low serum iron, ferritin levels, and vitamin D deficiency may be associated with ADHD.

Keywords: Attention deficit hyperactivity disorder, Case-control, Epidemiology, Iron deficiency, Risk factors, Vitamin D

Introduction

Attention deficit hyperactivity disorder (ADHD) is shown as one of the most common disorders in school-aged children.[1-6] ADHD has widespread effects on the functioning and development of affected children as well as having considerable impact on others including family members, peers, and teachers. It can lead to other disorders and academic difficulties and relationship and social functioning problems.[1-3,6] ADHD has also been shown to have long-term adverse effects on social-emotional development, vocational success and academic performance.[1-3,5,7-9] ADHD is the most prevalent neuropsychiatric disorder worldwide, in both developed and developing countries, affecting between 5% and 15% of school-aged children. The underlying pathophysiology of ADHD remains complex and not clearly understood.[8,9]

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Several studies[8-15] have attempted to understand the role of serum ferritin levels as a reliable measure of iron stores in body tissues, including the brain, in the absence of anemia in children with ADHD. Sever *et al.*,[11] studied the correlation between iron deficiency and ADHD and reported that supplementation of 5 mg/kg of iron to 14 ADHD children for 30 days resulted in increased serum ferritin level and reduced levels of ADHD on Conner's Rating Scale using standardized assessment tools.[4-6] It has been argued that ADHD is primarily caused by reduced serum iron concentration in view of significantly reduced serum iron levels in ADHD children.[9-16] Furthermore, genetic factors are known to be the dominant cause of ADHD,[5,8-10,17,18] and their interactions with environmental, and socioeconomical factors[9-12] produce a complex picture.

Iron deficiency is reported to be the most prevalent problem in the world today[19-23] and nutritional problem among children and there is there is considerable evidence iron is important for neurological functioning and development.[19] According to the World Health Organization, iron deficiency is the most prevalent nutritional deficiency. A 30% prevalence of iron deficiency anemia (IDA) at a minimum, has been noted among children, adolescents, and women in nonindustrialized countries, and iron deficiency is also the most prevalent nutritional deficiency in industrialized countries.[20,21] More recently study showed that the iron deficiency increased risk of psychiatric disorders, and attention deficit hyperactivity disorder, and developmental disorders.[20-23]

This is the first study to investigate the association between circulating iron serum, ferritin and vitamin D levels and ADHD and associated risk factors. This study, using a nationwide population-based database with a case-control method and the largest sample size, attempted to clarify the association between iron deficiency anemia and ADHD among children. We hypothesized that children with IDA exhibited the higher risk of having ADHD psychiatric disorder.

Subjects and Methods

This is a case-control study designed to determine the relationship between iron and vitamin D deficiency with ADHD in young Qatari population below 18 years of age who are visited Primary Healthcare Center (PHC), School Health or Pediatrics Clinic. With the available information[5] prevalence of ADHD is 15%, with 1% error bound and 99% confidence limit, power of the test considered to be 90% and the odds ratio 2, the required sample size was estimated as 630 cases and 630 controls would be sufficient to achieve the aim of the study. The data were collected between June 2011 and July 2013. A total of 630 cases of ADHD were matched with age, gender, and ethnicity of 630 control subjects.

The study was approved by the Hamad General Hospital, Hamad Medical Corporation. All human studies have been approved by the Research Ethics Committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All the parents of persons who agreed to participate in this study gave their informed consent prior to their inclusion in the study.

Data Collection

The ADHD children were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria confirming the presence of symptoms using Conners' Parents Rating Scale (CPRS) and Conners' Teachers Rating Scale (CTRS).[1-6,24-26] The inclusion criteria were children aged 6-18 years attending regular schools and not taking any medication or any stimulants.

Selection of attention deficit hyperactivity disorder subjects

The diagnosis of ADHD was based on physician-diagnosis. The CTRS was used to screen ADHD symptoms among children. [1-5,25-28] Teacher Rating Scales[6,24-26] are also an important part of the evaluation and diagnosis. Teacher Rating Scales provide necessary information about the child in the school setting. We used have used Swanson, Nolan, and Pelham (SNAP) questionnaire, SNAP-IV Teacher and Parent Rating Scale[24-26] and Conner's filled by both parents and teachers in addition to the clinical history and school performance. ADHD subjects aged below 18 years were identified from PHC Clinics and School Health as part of the cohort study of 630 ADHD series of children were approached which gave consent and participated in the study. The study excluded the subjects with following characteristics: Hemoglobin below 10 g/dL, Calcium supplements or vitamin D intake during the last 6 month before the study; history of epilepsy or antiepileptic drugs since they affect vitamin D; sun block use and the pubertal age since behavioral problems and 25(OH) D2 are affected by puberty and use of sun block.

Selection of controls

Control subjects aged below 18 years were identified from the community as healthy and as not been diagnosed as ADHD or if they never used any medication who are visited PHC or School Health. This group involved a matched consecutive series of 630 healthy subjects who visited the PHC Clinics for any reason other than acute or chronic disease subjects included, such as headache, etc., during the same period. The healthy subjects were selected in a way matching to the age, gender, and ethnicity of cases to give a good representative sample of the studied population.

Laboratory investigation

Blood collection and serum measurements of vitamin D

Trained phlebotomist collected venous blood sample, and serum separated and stored at -70°C until analysis. A blood test was carried out with the patient group and the control group, including the serum iron, ferritin, and hemoglobin, etc., Serum 25-hydroxyvitamin D [25(OH) D], a vitamin D metabolite, was measured using a commercially available kit (DiaSorin Corporate Headquarter, Saluggia, Italy). The treated samples were then assayed using competitive binding radio-immunoassay technique. Subjects were classified into four categories using traditional conventions: (1) *Severe* vitamin D deficiency, 25(OH) D < 10 ng/ml; (2) *moderate* deficiency, 25(OH) D 10-19 ng/ml; (3) *mild* deficiency, 25(OH) D 20-29 ng/ml; and (4) normal/optimal level is between 30 and 80 ng/ml.[27-28] Other baseline biochemical levels measured from the serum included vitamin D, calcium, magnesium, calcium, cholesterol, and phosphorus and parathyroid hormone levels on the basis of previous recommendations.[27-28] Serum levels of these biochemical parameters were determined according to standard laboratory procedures.

Assessment

The CPRS and CTRS were used[5,6,26-28] to screen ADH symptoms among children. Teacher Rating Scales[1-3,6,12] are also an important part of the evaluation and diagnosis. Teacher Rating Scales provide necessary information about the child in the school setting. The teacher also becomes a secondary informant who can judge the behavior of the child in the context of his peers.[1-3,9,26-28] The Conner's' Scale has been widely used in different settings and languages, and it has well-established reliability and validity across cultures.[27-28] The Conners' teacher scale contains 10 items for each of which the teacher was asked to indicate the degree of applicability to the child being assessed as follows: Not at all (score 0), just a little (score 1), much (score 2), and very much (score 3). For each child, we combined the item specific scores to obtain the total scores (maximum score of 30 and the minimum is 0). The score between 0-9 is seen as mild and 10-14 as moderate ADHD. Those who scored 15 or more were seen as having high levels of ADHD. The participants were interviewed by health professionals and nurses. The parents completed the second questionnaire which included the sociodemographic variables such as age, gender, nationality, level of education, and occupation of parents. The relationship of the consanguineous parents was recorded. In this study, Consanguinity was defined as marriages between relatives either first cousin or second cousin. Body mass index (BMI) was calculated as the weight in kilograms (with 1 kg subtracted to allow for clothing) divided by height in meters squared. BMI <85th percentile was considered normal weight, 85th-95th percentile as overweight and >95th percentile as obese.

The Student's *t* test was used to ascertain the significance of differences between mean values of two continuous variables and confirmed by nonparametric Mann-Whitney test. A Chi-square analysis was performed to test for differences in the proportion of categorical variables between two or more groups. Multiple logistic regression analysis using the forward inclusion and backward deletion method was used to assess the relationship between dependent (ADHD symptoms) and independent variables and to adjust for potential confounders and to order the importance of risk factors (determinant) for the ADHD. The level $P < 0.05$ was considered as the cut-off value for significance.

Results

Table 1 shows sociodemographic characteristics of the participants with ADHD and the controls. Of 630 of ADHD and 630 of healthy children were approached with their mean age (SD, in years) for ADHD and control children were 11.54 (3.83) versus 11.50 (3.62). There were statistically significant differences between ADHD and healthy children control subjects with respect to father education level ($P < 0.01$), occupation of father ($P < 0.01$), educational level of mother ($P < 0.01$), monthly income ($P = 0.03$), consanguineous marriages of parent ($P < 0.01$) and BMI in percentiles ($P < 0.01$).

Table 2 illustrates the comparison of family characteristics, child behavior, activities, and school performance of the two groups and all variables showed statistically significant differences.

Table 3 shows baseline chemistry biomarker values among the two groups. There were statistically significant differences between ADHD versus control children for vitamin D [16.81 (7.84) vs. 22.18 (9.00) ng/ml], serum iron [82.11 (13.61) vs. 85.60 (12.47) ng/ml], ferritin [36.26 (5.93) vs. 38.19 (5.61) ng/ml], hemoglobin [12.02 (2.13) vs. 12.89 (2.02) g/dL], magnesium [0.82 (0.08) vs. 0.88 (0.06) mmol/L], serum calcium level [2.35 (0.12) vs. 2.39 (0.14) mmol/L] and phosphorous [1.47 (0.30) vs. 1.54 (0.26) mmol/L]. The present study did not show any statistically significant differences between male and females regarding iron serum [males 83.35 (12.33) vs. females 84.57 (13.93) ng/ml; $P = 0.17$]. There was equal iron storage among male and females. Of total 630 of ADHD children, 116 (18.4%) had severe vitamin D deficiency (<10 ng/ml).

The predictors for ADHD in children using multivariate logistic regression analysis are shown in Table 4. The mean serum vitamin D level, serum iron, ferritin, serum calcium level, physical activity, nervous behavior, consanguinity, BMI, and child order were considered as the main factors associated with ADHD after adjusting for age, gender, and other variables.

Discussion

Although the present study includes a large sample size, as well as controls and physician-diagnosed ADHD and mental health illnesses a few limitations must be remembered prior to interpretation of our findings. The study does not have data on oral intake iron and vitamin D and the number of different types of ADHD was relatively small. Furthermore, this is a case-control study, which means that only associations can be identified, and not cause and effect.

Table 1: Sociodemographic characteristics of studied ADHD and control subject (*N*=1260)

Variables	*n* (%)		*P*
	ADHD symptoms children *N*=630	Control children *N*=630	
Age group (in years)			
5-10 years old	208 (33.0)	189 (30.0)	0.29
11-13 years old	199 (31.6)	224 (35.6)	
14-18 years old	223 (35.4)	217 (34.4)	
Sex			
Male	315 (50.0)	313 (49.7)	0.47
Female	315 (50.0)	317 (50.3)	
Nationality of student			
Qatari	319 (50.6)	325 (51.6)	0.38
NonQatari/Arabs	311 (49.4)	305 (48.4)	
Educational level of father			
Illiterate	22 (3.5)	20 (3.2)	<0.01
Primary	78 (12.4)	79 (12.5)	
Intermediate	132 (21.0)	122 (19.4)	
Secondary	212 (33.7)	231 (36.7)	
University and above	186 (29.5)	178 (28.3)	
Occupation of father			
Police/army/security	57 (9.0)	56 (8.9)	<0.01
Sedentary/professional	181 (28.7)	174 (27.6)	
Clerk	83 (13.2)	113 (17.9)	
Businessman	166 (26.3)	115 (18.3)	
Government officer	143 (22.7)	172 (27.3)	
Educational level of mother			
Illiterate	95 (15.1)	97 (15.4)	<0.01
Primary	105 (16.71)	126 (20.0)	
Intermediate	158 (25.1)	186 (29.5)	
Secondary	140 (22.2)	94 (14.9)	
University and above	132 (21.0)	127 (20.2)	
Occupation of mother			
Housewife	225 (35.7)	211 (33.5)	0.51
Sedentary/professional	133 (21.1)	162 (25.7)	
Clerk	133 (21.1)	150 (23.8)	
Businessman	139 (22.1)	107 (17.0)	
Monthly income ($ US Dollars)			
<$3000	200 (31.7)	194 (30.8)	0.03
$3000-$6000	218 (34.6)	259 (41.1)	
>$6000	212 (33.7)	177 (28.1)	
BMI group (percentile)			
<85th	544 (86.3)	500 (79.4)	<0.01
85th-95th	58 (9.2)	65 (10.3)	
>95th	28 (4.4)	65 (10.3)	
Consanguinity			
Yes	246 (39.0)	205 (32.5)	<0.01
No	384 (61.0)	425 (67.5)	
Exposure to sun	265 (42.1)	313 (49.7)	<0.01
Walking time/day<60 min	206 (32.7)	247 (39.2)	<0.01

ADHD: Attention deficit hyperactivity disorder, BMI: Body mass index

Table 2: Comparison of family characteristics and school performance by ADHD and control subjects

Variables	*n* (%)		*P*
	ADH symptoms children *N*=630	Control children *N*=630	
Physical activities			
Yes	276 (43.8)	342 (54.3)	<0.01
No	354 (56.2)	288 (45.7)	
Type of family			
Nuclear	394 (62.5)	450 (71.5)	<0.01
Extended	143 (22.7)	111 (17.6)	
More than one	91 (14.7)	691 (0.9)	
Multiple marriages			
Yes	104 (16.5)	62 (9.8)	<0.01
No	526 (83.5)	568 (90.2)	
Good relationship among parents			
Yes	568 (90.2)	599 (95.1)	<0.01
No	62 (9.8)	31 (4.9)	
Parents living together			
Yes	572 (90.8)	580 (92.1)	0.04
No	58 (9.2)	50 (7.9)	
Performance at school			
Excellent	205 (32.5)	212 (33.7)	0.03
Very good	212 (33.7)	198 (31.4)	
Good	122 (19.4)	155 (24.6)	
Average	91 (14.4)	65 (10.3)	
Obeys rule			
Yes	449 (71.3)	493 (78.3)	<0.01
No	181 (28.7)	137 (21.7)	
Noisy/hyperactive			
Yes	100 (15.9)	68 (10.8)	<0.01
No	530 (84.1)	562 (89.2)	
Cry for any reason			
Yes	101 (16.0)	49 (7.8)	<0.01
No	529 (84.0)	581 (92.2)	
Create problems and nervous			
Yes	82 (13.0)	54 (8.6)	<0.01
No	548 (87.0)	576 (91.4)	

ADHD: Attention deficit hyperactivity disorder, ADH: Attention deficit hyperactivity

Several studies have previously reported that children affected by ADH are at a high risk of developing comorbid disorders as well as impaired social adjustment. The potential difference in the prevalence of ADHD in western and nonwestern countries is related to biology, genetics, culture and family factors.[6,8] Furthermore, a degree of variation in prevalence rates may be attributable to the difference in the diagnostic criteria[3,10,11] though this is becoming more robust. More recently, the associations between iron serum and vitamin D deficiency and ADHD and their role on young children have not been reported in the literature.[8-16]

To the best of our knowledge, this is the first clinical study demonstrating abnormally low serum ferritin levels in children with ADHD in Arabian Gulf Countries. Serum ferritin levels were very low in children with ADHD compared to controls, this is consistent with the previous reported studies.[9-15] These levels in our study were extremely low in one-third cases indicating low iron stores. In contrast, serum ferritin levels in control children were within published normal ranges. Furthermore,

Table 3: Clinical biochemistry baseline value among ADHD and control subject

Variables	Reference normal value	ADHD	Control	P
		Mean±SD (N=630)		
Vitamin D (ng/ml)	30-80	16.81 (7.84)	22.18 (9.00)	<0.01
Serum iron (μg/dL)	37-158	82.11 (13.61)	85.60 (12.47)	<0.01
Ferritin (ng/ml)	15-150	36.26 (5.93)	38.19 (5.61)	<0.01
Hemoglobin (g/dL)	11.2-16.5	12.06 (2.13)	12.89 (2.02)	<0.01
Magnesium (mmol/L)	0.65-1.05	0.82 (0.08)	0.88 (0.06)	<0.01
Potassium (mmol/L)	3.4-4.7	4.62 (0.50)	4.57 (0.55)	0.21
Calcium (mmol/L)	2.10-2.5	2.35 (0.12)	2.39 (0.14)	<0.01
Phosphorous (mmol/L)	0.4-1.3	1.47 (0.30)	1.54 (0.26)	<0.01
		n (%)		
Supplement vitamin D		233 (37.0)	295 (46.8)	<0.01
Severe deficiency				
25(OH) D<30 ng/ml		116 (18.4)	78 (12.4)	<0.01

ADHD: Attention deficit hyperactivity disorder, SD: Standard deviation, 25(OH) D: 25-Hydroxyvitamin D

Table 4: Multivariate logistic regression analysis as predictors for ADHD children

Independent variables	Odds ratio	95% confidence interval	P
Vitamin D deficiency (ng/ml)	3.27	1.65-5.90	<0.01
Serum iron deficiency (ng/ml)	2.81	1.72-4.53	<0.01
Physical activity	2.67	1.68-4.26	<0.01
Ferritin (ng/ml)	2.53	1.81-3.45	<0.01
Serum calcium level	2.04	1.01-3.58	<0.01
Nervous behavior	1.73	1.14-2.56	<0.01
Consanguinity	1.49	1.16-1.92	<0.01
BMI in percentiles	1.38	1.15-1.54	<0.01
Child order	1.08	1.12-3.36	<0.01

BMI: Body mass index, ADHD: Attention deficit hyperactivity disorder

in many developed and developing countries, the majority of children who have ADHD are undiagnosed and there is limited recognition of child mental health problems in primary care.[1-3,5,6] Teachers and parents may be well placed to identify unrecognized children and to facilitate their referral to medical health care services hence the use of assessments by them become very important and relevant. The association between iron deficiency, ferritin deficiency and ADHD in young children have been previously reported in the literature but, the potential associated risk factors never been discussed.[9-24] Therefore, the current study conducted and explored an association between important circulating levels of iron deficiency, ferritin and vitamin D deficiency and their impact on ADHD and study outcome supported strong correlations among those variables.

As Konofal *et al*.,[14] had reported that iron deficiency has been previously considered a potent cause of poor cognitive impairment, learning disabilities, and psychomotor instability it is worth considering that iron deficiency (low serum ferritin level) could lead to ADHD symptoms in relationship with central dopaminergic dysfunction. Furthermore, iron supplementation[8-16,29] and vitamin D[21-24] may form a first-line treatment for children with ADHD and iron deficiency. Furthermore, Konofol *et al*.,[12] have shown that the mean serum ferritin levels, were lower in children with ADHD [mean (SD), 23 (13) ng/ml] than in the controls [mean (SD), 44 (22) ng/ml; $P < 0.01$], while serum iron, hemoglobin, and hematocrit levels were within normal ranges in both children with ADHD and controls and did not differ between groups and serum ferritin levels were inversely correlated with the severity of ADHD. They suggest that low iron stores may explain as much as 30% of ADHD severity. This correlation suggests that the iron deficient children are mainly inattentive and distractible and suffer from learning disabilities, a finding consistent with the role of iron deficiency in cognitive deficits and mental retardation.[30] Another aspect worth bearing in mind and further exploration is that the iron deficiency can be easily corrected. A causal relationship between iron deficiency and poor cognitive development and/or behavioral problems has been well-established over the past 3 decades.[29-33] Finally, there was a trend toward a correlation between the hyperactivity sub-scores and serum ferritin levels, the children with more severe iron deficiencies suffering from increased motor restlessness.[11] Previous studies have revealed that iron was associated with ADHD which affect the social-emotional development and functioning of children. In our study, an increased risk of ADHD was noted among those with IDA, which was compatible with a recent meta-analysis result.

More recently, a study from India[13] showed that serum ferritin levels newly diagnosed children with ADHD showed low levels of ferritin in comparison with controls-similar findings to the present study. There was also a significant inverse correlation between serum ferritin levels and oppositional subscores on Conner's Rating Scale. Our study also confirms findings from Israel.[9]

The current study suggests that low iron deficiency and ADHD pathophysiology could related to several multifactor. It is worth considering that iron deficiency (low serum ferritin level) could lead to ADHD symptoms in relationship with genetics, environmental risk factors, absence of iron supplementation, and lack of low nutritional foods. A causal relationship between iron deficiency and ADHD and poor cognitive development and/or behavioral problems has been well-established over the past 3 decades.[29-33] Previous studies have revealed that iron was associated with ADHD which affect the socioemotional development and functioning of children.[29,32]

The correct recognition of ADHD and prompt treatment has major international public health implications.[5,6] This study highlights standard laboratory assessments, which may give a clue toward the diagnosis and treatments. One important limitation is major diagnostic issues and implications of such diagnoses on children, teachers, peers, families and parents, and society at large must be explored further. Recognition of ADHD, even if accurate, may be harmful through labeling, stigmatization, scapegoating, and effects on self-perception. It has been argued that such over-medicalization enables both adults and children to avoid taking responsibility for a range of behaviors.[32] Current study revealed the importance of careful investigations and potential for early treatment for affected children and their families. Hyperactivity carries a considerable developmental risk even when considered in dimensional terms.

Although our study included a large sample of participants and it is case-controlled, it has some limitations. As confounding factors, we cannot exclude the possibility that they have contributed, to some extent, in determining the in the association of serum iron, ferritin levels, vitamin D, and ADHD. This study did not include data on children kept on avoidance/restriction diet. It is known that avoidance or restriction diet is one of the modalities of therapy in some case of ADHD and for a relatively short period of time. However, it is unlikely that the majority of ADHD patients in our study were on avoidance diet, or for prolonged time of dietary restrictions as the nutritional parameters (BMI) and laboratory biomarkers (serum iron, ferritin levels, and serum albumin) do not indicate evidence avoidance long enough to affect vitamin D status and iron deficiency. Hyperactivity and impulsivity are some of the main characteristic features of ADHD disease in children.

Conclusions

The association between lower serum levels of various factors needs to be explored further in longitudinal studies. This study indicates that low serum iron, ferritin levels and vitamin D deficiency may be associated with ADHD pathophysiology and therefore must be assessed. Furthermore in addition, education for the parents, teachers, families, and society at large is absolutely vital if the burden of disease related to ADHD is to be reduced. It may also be that various chemicals in the diet may be interfering with the absorption of various protectors and this must be explored as a matter of urgency.

What this study adds?

The correlation between iron, ferritin, vitamin D deficiency, and ADHD in young children has previously not been reported in the literature. However, data is lacking regarding the association between iron deficiency and ADHD. This study reveals that those deficiencies were higher in ADHD children compared with healthy children. Supplementing infants with iron and vitamin D might be a safe and effective strategy for reducing the risk of ADHD.

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References

1. Barbaresi WJ, Katusic SK, Colligan RC, Pankratz VS, Weaver AL, Weber KJ, *et al*. How common is attention-deficit/hyperactivity disorder? Incidence in a population-based birth cohort in Rochester, Minn. Arch Pediatr Adolesc Med 2002;156:217-24.
2. Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Jacobsen SJ. Long-term school outcomes for children with attention-deficit/hyperactivity disorder: A population-based perspective. J Dev Behav Pediatr 2007;28:265-73.
3. Biederman J, Monuteaux MC, Doyle AE, Seidman LJ, Wilens TE, Ferrero F, *et al*. Impact of executive function deficits and attention-deficit/hyperactivity disorder (ADHD) on academic outcomes in children. J Consult Clin Psychol 2004;72:757-66.
4. Clinical practice guideline: Diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. American Academy of Pediatrics. Pediatrics 2000;105:1158-70.
5. Sayal K, Daley D, James M, Yang M, Batty MJ, Taylor JA, *et al*. Protocol Evaluating the effectiveness of a school-based group programme for parents of children at risk of ADHD: The 'PArents, Teachers and CHildren WORKing Together (PATCHWORK)' cluster RCT protocol. BMJ Open 2012;2:pii: e001783 doi: 10.1136/bmjopen-2012-001783. Print 2012.
6. Bener A, Al Qahtani R, Teebi AS, Bessisso M. The prevalence of attention deficit hyperactivity symptoms in schoolchildren in a highly consanguineous community. Med Princ Pract 2008;17:440-6.
7. Sayal K, Hornsey H, Warren S, MacDiarmid F, Taylor E. Identification of children at risk of attention deficit/hyperactivity disorder: A school-based intervention. Soc Psychiatry Psychiatr Epidemiol 2006;41:806-13.
8. 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;38:965-80.
9. Lahat E, Heyman E, Livne A, Goldman M, Berkovitch M, Zachor D. Iron deficiency in children with attention deficit hyperactivity disorder. Isr Med Assoc J 2011;13:530-3.
10. Kwon HJ, Lim MH, Ha M, Kim EJ, Yoo SJ, Kim JW, *et al*. Transferrin in Korean children with attention deficit hyperactivity disorder. Psychiatry Investig 2011;8:366-71.
11. Sever Y, Ashkenazi A, Tyano S, Weizman A. Iron treatment in children with attention deficit hyperactivity disorder. A preliminary report. Neuropsychobiology 1997;35:178-80.
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. Juneja M, Jain R, Singh V, Mallika V. Iron deficiency in Indian children with attention deficit hyperactivity disorder. Indian Pediatr 2010;47:955-8.
14. 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;38:20-6.

15. 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.
16. Menegassi M, Mello ED, Guimarães LR, Matte BC, Driemeier F, Pedroso GL, *et al*. Food intake and serum levels of iron in children and adolescents with attention-deficit/hyperactivity disorder. Rev Bras Psiquiatr 2010;32:132-8.
17. 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.
18. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, *et al*. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57:1313-23.
19. Beard J. Iron deficiency alters brain development and functioning. J Nutr 2003;133 5 Suppl 1:1468S-72.
20. World Health Organization. Iron deficiency anaemia: Assessment, prevention and control. a Guide for Programme Managers. Geneva: World Health Organization; 2001.
21. 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.
22. Cortese S, Angriman M, Lecendreux M, Konofal E. Iron and attention deficit/hyperactivity disorder: What is the empirical evidence so far? A systematic review of the literature. Expert Rev Neurother 2012;12:1227-40.
23. Halterman JS, Kaczorowski JM, Aligne CA, Auinger P, Szilagyi PG. Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States. Pediatrics 2001;107:1381-6.
24. Conners CK. Conner' Rating Scales-Revised. North Tonawada, NY: Multi-Health System Publishing; 1997.
25. Miller ML, Fee VE, Netterville AK. Psychometric properties of ADHD rating scales among children with mental retardation I: Reliability. Res Dev Disabil 2004;25:459-76.
26. Swanson JM, Nolan W, Pelham WE. The SNAP-IV Rating Scale (PDF), 1992. APA Division 16 School Psychology 62 (3): 93-98. Retrieved 2009-02-16.
27. Bener A, Al-Ali M, Hoffmann GF. High prevalence of vitamin D deficiency in young children in a highly sunny humid country: A global health problem. Minerva Pediatr 2009;61:15-22.
28. Tan LN, Wei HY, Zhang YD, Lu AL, Li Y. Relationship between serum ferritin levels and susceptibility to attention deficit hyperactivity disorder in children: A meta analysis. Zhongguo Dang Dai Er Ke Za Zhi 2011;13:722-4.
29. McCann JC, Ames BN. An overview of evidence for a causal relation between iron deficiency during development and deficits in cognitive or behavioral function. Am J Clin Nutr 2007;85:931-45.
30. Logoff B, De Andraca I, Castillo M, Smith JB, Walter T, Pino P. Behavioral and developmental effects of preventing iron-deficiency anemia in healthy full-term infants. Pediatrics 2003;112:846-54.
31. Timimi S, Taylor E. ADHD is best understood as a cultural construct. Br J Psychiatry 2004;184:8-9.
32. Lozoff B, Georgieff MK. Iron deficiency and brain development. Semin Pediatr Neurol 2006;13:158-65.
33. Beard JL. Why iron deficiency is important in infant development. J Nutr 2008;138:2534-6.

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