Published in final edited form as:
Pediatr Int. 2012 October ; 54(5): 688–692. doi:10.1111/j.1442-200X.2012.03664.x.

Ferritin and Hyperactivity Ratings in Attention Deficit Hyperactivity Disorder

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Abstract

Background—Iron is a co-factor of tyrosine hydroxylase which is a critical enzyme in dopamine synthesis. Dopamine has been implicated in the pathophysiology of ADHD. Our objective was to investigate the association of ferritin level with parent and teacher ratings and cognitive measures after controlling for age, gender, ADHD subtype, comorbid conditions, hemoglobin, mean corpuscular volume and reticulosite distribution width in a large sample.

Methods—The study included 713 children and adolescents with ADHD (613 males; age 7–15). Conners Parent Rating Scale (CPRS) and Conners Teacher Rating Scale (CTRS) were obtained. In a subgroup of patients we conducted Digit Span, Digit Symbol, Trail Making Tests as measures of attention and executive functioning.

Results—Multiple regression analysis indicated that CPRS Hyperactivity score was significantly associated with ferritin level (B=−.12; t=−3.1; p:.002). Other CPRS and CTRS scores as well as cognitive measures were not associated with ferritin level.

Conclusions—Although it is not possible to make an inference on causality in cross-sectional studies, the results of this largest scale cross-sectional field study to date suggest that lower ferritin level might be associated with parent-reported hyperactivity after controlling for important confounding factors.

Keywords

attention deficit hyperactivity disorder; ferritin; hyperactivity; parent; symptoms

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There are no conflicts of interest.

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders of childhood and adolescence. There are currently three subtypes of ADHD: combined, inattentive and hyperactive-impulsive, as defined by the DSM-IV-TR criteria[1]. The exact pathophysiology of ADHD symptoms remains unclear, although several converging lines of investigation suggest that both genetic and environmental factors, and their interactions, are important. An emerging interest of research in recent years has been the investigation of a possible association of iron metabolism as a risk factor for ADHD. To date, although a number of studies have shown that children with ADHD have lower mean ferritin levels when compared with normal controls, and that low serum ferritin levels are related with more severe ADHD ratings, as reported by teachers and/or parents [1–5], other studies have also reported negative findings[6–7] . Understandably, a number of studies have also focused on the utility of iron supplementation in ADHD; these studies have yielded conflicting results[8–9]. It has also been shown that iron deficiency during infancy might lead to learning and memory problems, which might also have enduring effects in grade-school period[10]. In a relatively small sample, we previously reported that there were no significant correlations between ferritin level and performance in vigilance and sustained attention tasks, executive function tests like planning and organization, complex problem solving, set shifting, and response monitoring[3]. In another distinct sample, we also showed that presence of comorbid conditions might also increase the effect of lower iron stores on behavioral measures[11]. However, the sample size of this latter study did not allow us to control for the effects of ADHD subtype as well as different comorbid conditions on parent and teacher ratings.

In this study, our aim was to investigate the relationship between age, gender, ferritin level, hemoglobin, mean corpuscular volume (MCV), reticulosite distribution width (RDW) with parent and teacher reports and cognitive measures in a large sample of children and adolescents with ADHD. The control of ADHD subtype and specific comorbid condition categories is important since it has been shown that both are associated with symptom ratings[12–13]. We therefore also controlled for confounders including ADHD subtype (combined, inattentive, hyperactive-impulsive), presence of comorbid conditions (grouped into four: anxiety disorders, oppositional defiant/conduct disorder, learning disabilities and other conditions including tic disorders, elimination disorders, and mood disorders). We selected the hematological variables since iron deficiency is usually defined by low serum ferritin levels, or low MCV and high RDW values. We also selected Digit Span, Digit Symbol and Trail Making Test Part A as attentional indices. Based on our prior findings, we predicted that after controlling for the above mentioned variables, parent and teacher reported hyperactivity ratings would be negatively associated with ferritin level. We also predicted that ferritin level would not be significantly associated with attention problems ratings and cognitive measures.

Methods

Seven hundred thirteen subjects with ADHD (613 males and 100 girls; age 7–15, mean ±standard deviation: 9.1±2.2) were included in the study. All subjects were recruited among consecutive referrals to three ADHD clinics that are part of a general child psychiatry outpatient department in a major municipal pediatric hospital. All the subjects with primary attentional, hyperactivity and behavioral concerns were referred to specific ADHD clinics where differential diagnosis and all other relevant clinical evaluations took place. The inclusion criteria were ADHD diagnosis per DSM-IV criteria; being drug free at least for 15 days; and an age range 7–15 years. We excluded all children and adolescents who were currently on any ADHD medications since medication exposure is likely to alter parent and teacher ratings and it was important to obtain uniformity with unbiased by knowledge of treatment. We also excluded subjects whose parents/teachers did not fill in the rating scales or filled in incompletely. Diagnosis was made by the authors (PO, OO, EC) who are all experienced child psychiatrists certified in the use of the Turkish-version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children — Present and Lifetime Version (K-SADS-PL) semi-structured interview which has shown to be a valid diagnostic measure adapted for the Turkish language[14–15]. The study was approved by the institutional ethics committee. Informed consent process was verbal as is customary given the literacy level of the parents. The parents could select to opt out of the study, but none of the parents refused to do so. All the subjects who participated in the study were Caucasian. All cases had unremarkable medical history, other than ADHD, and were assessed for anxiety disorders, mood disorders, oppositional defiant disorder/conduct disorder, tic disorders and elimination disorders with corresponding K-SADS-PL modules. Learning disabilities were also evaluated with the use of the Turkish-version of the Weschler Intelligence Scale for Children- Revised (WISC-R) and reading, writing and mathematics tasks.

Symptom severity was evaluated by means of the Conners Parent and Teacher Rating Scales.

Conners Parent Rating Scale (CPRS)

This form includes 48 items, which aims to evaluate behavior of children assessed by their parents[16]. The scale includes oppositional behavior, inattentiveness, hyperactivity, psychosomatic and irritability domains. Turkish translation has good validity and reliability[17].

Conners Teacher Rating Form (CTRS)

This form includes 28 items, which aim to rate classroom behavior of children assessed by teachers[18]. There are three subscales of the form: 8 items inattentiveness, 7 items hyperactivity and 8 items conduct problems. CTRS is translated to Turkish by Şener [19], and the Turkish form showed adequate validity and reliability (Cronbach's alpha .95).

Cognitive Measures

Wechsler Intelligence Scale for Children- Revised form (WISC-R)—WISC-R is consisted of 12 subtests, which assessed verbal and performance abilities. Verbal subtests are Information, Similarities, Vocabulary, Comprehension and Digit Span. Performance subtests are Picture completion, Picture Arrangement, Block Design, Object Assembly, and Digit Symbol. Verbal and Performance IQ scores are obtained from the test. The reliability and validity studies of the Turkish form were conducted[20]. While WISC-R is a relatively outdated form of the test, it is widely used, and we do not have updated forms translated into Turkish. Digit Span and Digit Symbol tests were applied to 694 subjects.

Trail making test A—The basic task is connecting a series of stimuli (numbers expressed as numerals) in a specified order as quickly as possible. The score is the number of seconds required to complete the task. Trail making test performance is heavily influenced by attention. Test takes 5 to 12 minutes. Higher scores in these two tests indicate worse performance. We used Comprehensive Trail-Making Test[21]. We obtained TMT A results from 606 subjects.

The hematological profile including hemoglobin (Hgb), mean corpuscular volume (MCV), red cell distribution width (RDW) parameters were determined using COULTER® GEN·S™ system (COULTER® Corp, Miami, USA).The serum ferritin was measured by a solid-phase, 2-site chemiluminescent immunometric assay (Immulite 2000™; Diagnostic Products®, Los Angeles, CA).

Since satiety effects iron level and ferritin level changes with acute infections, fasting blood was drawn from each patient, always between 08:30 am–10:30 am in the morning. Blood was drawn from patients with acute infections at least 15 days after the infection with the control of clinical sign and symptoms and sedimentation rate.

Data Analysis

We compared ferritin level of different groups (males vs. females; subtypes; comorbid conditions; good treatment response vs. others) with one-way analysis of variance. Multiple regression analysis was used in order to evaluate the effects of age, gender, ferritin, and hemoglobin levels, MCV and RDW values, ADHD subtype (combined, inattentive, hyperactive-impulsive), and comorbidity (anxiety disorders, oppositional defiant/conduct disorder, learning disabilities, and other conditions) on: the CPRS and CTRS Attention Problems and Hyperactivity scores; WISC-R Digit Span and Digit Symbol subtest scores; and the TMT A score. For hematological indices, we chose ferritin, hemoglobin; MCV and RDW values since they were the factors evaluated in anemia and iron deficiency criteria. Model fit in the regression analysis was evaluated by Durbin-Watson test. Two-tailed significance tests ($p<.05$) are reported throughout. For regression analysis B (regression coefficient) and t (t value for the B), and corresponding p values were reported. SPSS 13.0 statistical package was used for the analysis.

Results

We had a total of 884 subjects eligible for the study, 171 of these subjects were not included in the study either due to lacking data on hematological variables, behavioral and/or cognitive measures. Data obtained from 713 subjects were analyzed. In this final study group, 466 (65.6%) of the subjects had combined subtype ADHD while 115 (16.2%) and 129 (18.2%) had inattentive and hyperactive-impulsive subtypes, respectively. Only 20.6% (n=147) of the study subjects uniquely had ADHD; 39.6% (n=282) had one comorbid condition; 29.6% (n=211) had two and 10.2% (n=73) had three or more comorbid conditions. The most frequent comorbid condition was oppositional defiant/conduct disorder (44.7%) followed by learning disabilities (27.1%) and anxiety disorders (15.6%). Mean ferritin level was 29.6 ng/ml with a standard deviation of 14.8 ng/ml; 9.7% of the subjects had ferritin lower than 12 ng/ml and 48.4% had lower than 25 ng/ml.

Descriptive data on CPRS, CTRS, cognitive test scores and hematological variables are reported in Table 1. Ferritin level was not significantly different between males and females, ADHD subtypes and subjects with or without comorbidity (results are not shown). Correlation analysis was summarized in Table 2. As evident from the table ferritin level was significantly associated with higher CPRS Hyperactivity score (p=.005). There was also a trend for association between Digit Span and ferritin level (p=.05). Multiple regression results indicated that CPRS Hyperactivity score was significantly associated with ferritin level (B=−.15; t=−3.4; p=.001, Table 3). The association between CTRS Hyperactivity score and ferritin level was in the same direction but not significant (B=−.05; t=−1.3). Other CPRS and CTRS scores as well as cognitive measures were not associated with ferritin level.

As summarized in Table 3, age was negatively associated with CTRS Hyperactivity, TMT-A, Digit Span and Digit symbol scores. Being male was associated with CTRS Hyperactivity and Attention Problems scores. Oppositional defiant/conduct disorder comorbidity was associated with higher CTRS Behavioral Problems and CPRS Hyperactivity and Attention Problems scores. Learning disability was associated with higher CTRS Attention Problems, TMT-A, Digit Span and Digit symbol scores. Subjects with anxiety disorders comorbidity had lower CTRS Hyperactivity and Attention Problems scores.

Discussion

In a large sample of children and adolescents with ADHD, controlling for age, gender, ADHD subtype, and comorbid conditions our results showed that there was a significant negative association between parent-reported hyperactivity ratings of ADHD and ferritin level. However, it must be noted that, while significant, the association was not strong. The weak association suggested that only a very small fraction of the parent reported hyperactivity symptoms could be understood by investigating ferritin levels. Besides, the relationship between ferritin level and teacher-reported hyperactivity ratings was not statistically significant, further suggesting that the association between ferritin and hyperactivity is not very strong. On the other hand, this could also be due to the measures used: objective measures of activity might produce different results than scale scores. We found no significant associations between ferretin levels and parent or teacher reported attention problems. We also did not find a significant association with cognitive measures and ferritin level.

The result of this present research is consistent with previous studies that have shown that reduced ferritin level is associated with higher parent[3,5,11], or teacher hyperactivity ratings. In this current study, as also in our previous research, we did not find any association between reduced ferritin level and attention problems as measured by either parent and teacher reports[5] or cognitive tests[3]. It is not readily intuitive to interpret the differences between parent and teacher reports. It has been known that parent and teacher reports have a correlation of only .30, and parents and teachers do not necessarily endorse the same types of behavioral problems. Nevertheless, the association of reduced ferritin level with higher parental endorsement of hyperactivity symptoms among children and adolescents with

ADHD may possibly signify a higher threshold of severity of hyperactivity, as teachers are more likely to more uniformly endorse symptoms of hyperactivity across all DSM-IV-TR ADHD subtypes. In future studies, more subtle differences between parent and teacher reports of hyperactivity should be studied to evaluate such differences. Furthermore, as the cognitive assessments we utilized in this study were by no means exhaustive; therefore we cannot rule out significant associations among other cognitive measures with ferritin level.

The current research is important in that it replicates the work for a much larger carefully assessed sample of children and adolescents using structured diagnostic measures, ADHD checklists and cognitive tasks. The findings of the present study, comprising children and adolescents without clinical iron deficiency, are not consistent with studies which reported that for those children presenting with iron deficiency learning and memory impairments can indeed persist up to school years [10,22]. The most important difference between the present study and those previous studies was that our sample mostly consisted of school-age children and adolescents without clinical iron deficiency. The negative association of ferritin level as a risk condition for ADHD needs to be understood in terms of its pathophysiology. Nevertheless, this first needs to be distinguished from effects of persistent clinical iron deficiency on learning and cognition.

While the pathophysiology of ADHD remains unclear, brain imaging studies, mechanism of action of stimulant medication, functional imaging findings on dopamine transporter protein, and molecular gene studies, provide support for altered dopaminergic transmission[23]. It has been found that iron is closely related to dopamine metabolism, being a coenzyme of tyrosine hydroxylase, and that D2 and D4 receptor and dopamine transporter densities decrease with decreased brain iron levels[24–26]. Iron deficiency is associated with decreased dopamine transporter expression[27]; and variation in the dopamine transporter gene has been linked to genetic vulnerability for ADHD[28]. Iron content is highest in globus pallidus, nucleus ruber, substantia nigra and putamen[29], and iron deficiency may lead to dysfunction in the basal ganglia[30], which are believed to play a significant role in the pathophysiology of ADHD[31]. Iron has an essential role in myelin deposition by oligodendrocytes[32] and iron deficiency impairs myelination[33]. It can be speculated that changes in brain iron level might cause further alterations in brain dopaminergic system[34], which seems to be already impaired in ADHD subjects[35]. Ferritin level in most of our sample was higher than 12 ng/ml, therefore our results suggested that decreased iron storage even when there is no clinical iron deficiency might contribute to more prominent hyperactivity symptoms.

The findings need to be interpreted in the context its limitations. Foremost, it must be stressed that cross-sectional association studies do not provide information on causality and that iron deficiency, at best, may be considered a risk factor for ADHD, only in a subsample of subjects. Second, using an objective method to measure activity level might produce different results.

As expected, the teacher hyperactivity ratings were endorsed at a higher rate for boys, consistent with both epidemiological and clinical findings. In a meta-analysis, Gershon showed that girls with ADHD had lower hyperactivity and impulsivity ratings[36]. Subjects with oppositional defiant/conduct disorder comorbidity had higher behavioral problems ratings obtained from both parents and teachers; parents also reported more attention problems and hyperactivity in this group. Previous studies have shown that ADHD subjects with comorbid conduct problems had more severe symptoms on parent and teacher ratings[13]. Subjects with anxiety disorder had lower behavioral problems score, which was also consistent with the previous reports[37]. Presence of learning disability was associated with higher teacher reported attention problems, and lower TMT and Digit Span and Digit Symbol performance.

Conclusion

This report represents the largest sample, to date, of children and adolescents, among whom the parent hyperactivity ratings were significantly negatively associated with ferritin level after controlling for age, gender, ADHD subtype, and comorbid conditions. Ferritin level was not associated with attention problems ratings or cognitive tests. Although it is not possible to make a statement on causality, the results of this cross-sectional study suggest that lower ferritin level may be a risk factor for parent-reported hyperactivity.

Acknowledgement

Ozgur Oner and Pinar Oner were supported by NIMH Fogarty International MHDD Training Program (D43TW05807) at Children's Hospital, Boston.

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Table 1

Mean±standard deviation (SD) of Conners Teacher Rating Scale (CTRS) and Conners Parent Rating Scale (CPRS) scores, cognitive test scores and hematological variables

	Minimum-Maximum	Mean±S. D.
CTRS hyperactivity	0–18	8.5±3.6
CTRS attention problems	0–31	10.6±3.9
CPRS hyperactivity	0–12	8.3±2.9
CPRS attention problems	0–15	7.2±2.9
Trail making test A (time in seconds)	21–312	96.9±52.2
Digit span	0–15	7.6±2.8
Digit symbol	1–19	8.7±3.3
Ferritin (ng/ml)	2.9–91.5	29.6±14.8
Hemoglobin (g/dl)	9.8–15.9	13.4±.96
*MCV (fl)	55–92	80.4±6.4
†RDW (%)	7.8–17.0	12.6±.93

*MCV, mean corpuscular volume

†RDW, red blood cell distribution width

Table 2

Pearson correlations of ferritin level with scale scores and cognitive variables.

	CPRS Hyperactivity	CPRS Inattention	CTRS Hyperactivity	CTRS Inattention	Trail Making Test- A	WISC-R Digit Symbol	WISC-R Digit Span
Ferritin	−.110*	−.058	−.008	−.052	−.010	.024	.075**

CPRS: Conners Parent Rating Scale, CTRS: Conners Teacher Rating Scale, WISC-R: Weschler Intelligence Scale for Children, Revised. LD:

* p<.01,

** p=.05

Table 3

Multiple linear regression results.

	Dependent Variables													
	CPRS Hyperactivity		CPRS Inattention		CTRS Hyperactivity		CTRS Inattention		Trail Making Test- A		WISC-R Digit Symbol		WISC-R Digit Span	
Independent Variables	**Beta**	**t**	**Beta**	**t**	**Beta**	**t**	**Beta**	**t**	**Beta**	**t**	**Beta**	**t**	**Beta**	**t**
Gender	−.07	−1.8	−.01	−.31	−.13	−3.2*	−.10	−2.5**	.01	.31	.09	2.4**	.01	.14
Age	−.06	−1.6	.01	.18	−.18	−4.4*	−.08	−1.9	−.50	−13.3*	−.18	−4.6*	−.15	−3.8*
Hgb	−.01	−.21	.02	.50	−.01	−.14	−.06	−1.4	.01	.20	.01	.35	.02	.58
MCV	.02	.45	−.01	−.08	.06	1.4	.09	2.1**	.04	.88	−.01	−.18	−.01	−.22
RDW	−.05	−1.2	−.01	−.25	.01	.19	−.01	−.13	.07	1.9	−.04	−.94	−.04	−.84
Ferritin	−.12	−3.1*	−.05	−1.4	−.05	−1.3	.01	.12	.01	.26	.01	.22	.06	1.6
Subtype	−.04	−1.1	−.09	−2.4	.03	.63	−.01	−.29	−.02	−.40	−.03	−.79	−.02	−.50
Anxiety	−.06	−1.5	−.08	−1.9	−.11	−2.9*	−.08	−2.1**	.01	.09	.06	1.5	.06	1.5
LD	−.08	−2.0	.01	.24	−.05	−1.2	.10	2.4**	.07	2.0**	−.12	−3.2*	−.25	−6.6*
ODD/CD	.20	5.2*	.13	3.3*	.06	1.4	.03	.84	.01	.30	.00	−.01	−.04	−1.1

CPRS: Conners Parent Rating Scale, CTRS: Conners Teacher Rating Scale, Hgb: hemoglobin, MCV:mean corpuscular volume, RDW: red cell distribution width, WISC-R: Weschler Intelligence Scale for Children, Revised. LD: Learning Disorder, ODD/CD: Oppositional Defiant Disorder/Conduct Disorder.

* $p<.01$;

** $p<.05$.