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Relationship of Ferritin to Symptom Ratings Children with Attention Deficit Hyperactivity Disorder: Effect of Comorbidity

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Abstract

Our aim was to investigate the relation between behavioral symptoms and hematological variables which are related with iron deficiency and anemia, ferritin, hemoglobin, mean corpuscular volume (MCV), and reticulosite distribution width (RDW) in children and adolescents with pure Attention Deficit Hyperactivity Disorder (ADHD) or ADHD comorbid with other psychiatric disorders. The sample consisted of 151 subjects with ADHD, 45 of these subjects had other comorbid conditions. Conners Parent (CPRS) and Teacher Rating Scales (CTRS) were obtained. Comorbid ADHD subjects had lower mean hemoglogin and MCV. In the ADHD group in general, CPRS and CTRS Total scores were significantly negatively correlated with ferritin level. When only pure ADHD subjects were taken into account, the correlations did not reach statistical signifance. Overall, these results suggested that lower ferritin level was associated with higher behavioral problems reported by both parents and teachers. Presence of comorbid conditions might increase the effect of lower iron stores on behavioral measures.

Keywords

Attention Deficit Hyperactivity Disorder; Ferritin; Comorbidity

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neuropsychiatric disorders of childhood, consisting of two symptom domains, hyperactivity/impulsivity and inattentiveness [1]. The exact pathophysiology of the symptoms is unclear at the moment in spite of numerous studies conducted with children with ADHD have been published each year, However, many studies using different methodologies, including animal, genetics, and neuroimaging studies, have indicated that dopamine is a key element of ADHD pathophysiology. Rats with lesions involving the ventral tegmental area (VTA) have hyperactivity and problems in focusing on specific stimulus. These animals also have difficulties in shifting behavior [2]. Similarly, cortical dopamine (DA) deficiency causes hyperactivity, problems in inhibition, spatial orientation and temporal organization. The changes in prefrontal cortical areas also lead to reactive changes of the subcortical

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dopaminergic system [3]. These studies indicate that dopamine may have an important role on all of the main symptom domains of ADHD. Some authors suggested that the lack of efficient dopaminergic control in the cortical and limbic striatal areas might result in selective attention and behavioral inhibition [4, 5]. ADHD is associated with genetic alterations in dopamine transporter gene, dopamine receptor 4 and 5 genes [6]. Positron Emmision Tomography studies have shown that the main target of the stimulants, which constitute the first-line of ADHD treatment, is the dopamine transporter [7]. These results also suggests a strong link between dopaminergic impairment and ADHD. However, with current knowledge, it is not easy to establish the causation relationship between dopaminergic alterations and ADHD.

Iron is a coenzyme of tyrosine hydroxylase, which is critical in dopamine synthesis [8]. Iron is also related with monoamine oxidase, which is critically related with degradation of dopamine. Iron is colocalized with dopaminergic neurons in the brain [8] and D2 and D4 receptor and dopamine transporter densities decrease with decreased brain iron levels [9, 10]. All these results suggest that iron metabolism may have important role in ADHD pathophysiology. One study showed that children with ADHD had lower mean ferritin levels when compared with normal controls and that low serum ferritin levels were related with more severe symptoms as indicated by higher Conners Parent Rating Scale scores [11]. Other studies have focused on the utility of iron supplementation in ADHD, with conflicting results [11]. One study investigated the relationship between iron levels and cognitive functioning of children with ADHD [12]. Results of that study reported 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. However, no study to date has investigated the effects of comorbidity on the relationship between ferritin levels and symptoms in subjects with ADHD. This is rather surprising since comorbidity is very common in ADHD [13].

In this study, our aim was to investigate the effects of comorbidity on the relationship between ferritin, hemoglobin, mean corpuscular volume (MCV) and reticulosite distribution width (RDW) and behavioral symptoms of children and adolescents with ADHD. We selected these variables since iron deficiency is usually defined by low serum ferritin levels, or low MCV and high RDW values. Presence of comorbidity may effect the severity, course and the treatment of the psychopathology [14]. As mentioned above, iron deficiency is also associated with worse symptom ratings in children with ADHD. Therefore, our hypothesis was that behavioral symptoms of subjects with ADHD were related to ferritin level and the relation might be more prominent in comorbid subjects.

Method

Population and Sampling

The sample consisted of 151 subjects with ADHD (127 boys, 24 girls; age 5–16; mean ± SD = 9.9 ± 2.8). Of 151 ADHD subjects 45 subjects had other comorbid conditions (32 boys, 13 girls; age 5–16; mean ± SD = 9.1 ± 2.7). These comorbid conditions included intellectual disability and learning disorders, anxiety disorder, tic disorder, elimination disorders, depression and conduct disorder. All of the subjects were Caucasian. All subjects were recruited from the general outpatient clinic of a general hospital, who fulfilled the inclusion criteria. ADHD diagnosis was based on DSM-IV criteria and made by the first and second authors, using K-SADS-PL semi-structured interview. All ADHD subjects had unremarkable medical history other than ADHD and were clinically screened for psychosis, eating disorders, substance use disorders, pervasive developmental disorders, and mental retardation. All patients were diagnosed for the first time and had never been evaluated for psychiatric disorders or treated with psychopharmacological medicine. 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 participate.

Symptom Severity was Evaluated with 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 [15]. The scale includes oppositional behavior, inattentiveness, hyperactivity, psychosomatic and irritability domains. Turkish translation has good validity and reliability [16].

Conners Teacher Rating Form (CTRS)—This form includes 28 items, which aim to rate classroom behavior of children assessed by teachers [17]. There are three subscales of the form: 8 items inattentiveness, 7 items hyperactivity and 8 items conduct problems. CTRS is translated to Turklish by Şener [18], and the Turkish form showed adequate validity and reliability (Cronbach's alpha .95).

Serum ferritin, hemoglobin, MCV and RDW values were measured in the morning in fasting blood. Iron deficiency was defined as ferritin <12 ng/ml or MCV <70 fL and RDW >14.5. Anemia was defined as serum hemoglobin <11.0 g/dl. All patients with iron deficiency or anemia were referred to pediatricians for treatment.

Analysis

CPRS-CTRS Total scores, ferritin, hemoglobin, MCV and RDW values obtained from subjects with pure or comorbid ADHD were compared with analysis of variance. Correlations between behavioral measures and ferritin level was computed by using Pearson correlation coefficients. Multiple regression analysis was used in order to evaluate the effects of age, gender, ferritin and hemoglobin levels, mean corpuscular volume and RDW values, and presence of comorbid conditions on the CPRS-CTRS Total scores. We chose ferritin, hemoglobin; mean corpuscular volume and RDW values since they were the factors evaluated in anemia and iron deficiency criteria. Frequency of iron deficiency in pure or comorbid ADHD subjects was compared with chi-square test. Two-tailed significance tests ($p < .05$) are reported throughout. SPSS 13.0 statistical package was used for the analysis.

Results

Effects of Comorbidity

ADHD subjects with comorbidity had significantly lower hemoglobin ($F(1,147) = 12.1$; $p = .001$) and MCV $F(1,147) = 5.9$; $p = .016$) when compared with pure ADHD subjects. There were no significant differences for CPRS and CTRS Total scores, ferritin and RDW (Table 1).

Correlations of Behavioral Problems and Ferritin Level

Whole ADHD Group—In the whole ADHD group, CPRS and CTRS Total scores were significantly negatively correlated with ferritin level ($r = -.17$; $p = .047$ and $r = -.22$; $p = .014$, respectively).

Pure ADHD Group—When only pure ADHD subjects were taken into account, while CPRS and CTRS Total scores were continued to be negatively correlated with ferritin level, these did not reach statistical signifance ($r = -.19$; $p = .064$ and $r = -.09$; $p = .361$, respectively).

Comorbid ADHD Group—There was a significant inverse correlation between CTRS Total score and ferritin level when only the comorbid ADHD subjects were taken into account ($r = -.39$; $p = .011$), while the correlation between CPRS and ferritin level was not significant ($r = -.12$; $p = .438$).

Linear Regression Results

Linear regression results are summarized in Table 2. The model significantly predicted CTRS Total score ($F = 2.74$; $p = .012$). CTRS Total score was significantly related with ferritin level; subjects with lower ferritin levels had higher scores, indicating more severe problems ($B = -.27$, $t = -2.8$, $p = .006$). Younger subjects tended to have higher CTRS Total score ($B = -.22$, $t = -1.9$, $p = .052$). Presence of comorbidity was not a significant factor. The effect of gender was not significant ($B = -.12$, $t = -1.26$, $p = .21$).

The model did not significantly predicted CTRS Total score ($F = 1.60$; $p = .14$). CPRS Total score was significantly related with MCV; subjects with lower MCV had higher scores, indicating more severe problems ($B = -.22$, $t = -2.1$, $p = .046$). Presence of comorbidity or ferritin level was not significant. The effects of age ($B = -.07$, $t = -.69$, $p = .49$) and gender ($B = -.13$, $t = -1.35$, $p = .18$) were not significant.

Iron Deficiency

About 9 subjects had iron deficiency. The frequency of iron deficiency was not significantly different between subjects with pure ADHD (5.9%) or with comorbid conditions (7.0%) ($\times 2 = .06$, $p = .73$).

Discussion

To our knowledge, this is the first study investigating the effect of comorbidity on the relationship between ferritin level and behavioral problems reported by the parents and teachers in ADHD subjects. Consistent with this previous studies [11, 19], we found that lower ferritin levels were associated with higher problem scores. 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 [8–10]. It can be speculated that iron deficiency may cause further alterations in brain dopaminergic system, which seems to be already impaired in ADHD subjects [20]. It has been proposed that there might be multiple developmental pathways for ADHD that includes different neuropsychological subtypes [21]. It is not clear whether iron deficiency is differentially related to any specific developmental pathway and the underlying neural substrate, and this must be evaluated in future studies.

Comorbidity is frequent in ADHD. The most frequent comorbid conditions include oppositional defiant disorder, conduct disorder, anxiety disorders, mood disorders and learning disorders [13]. Comorbidity is more common in males and type of comorbidity may change with age. Anxiety and depression symptoms are more common in adolescents with untreated ADHD when compared with younger subjects [22]. Presence of comorbid conditions might effect the severity of psychopathology, long-term course of the disorder and treatment response [13]. Severity of the ADHD symptoms, presence of comorbidity and adverse conditions predict the persistence of ADHD into late adolescence [23]. Thus, comorbid conditions must be evaluated in all ADHD subjects. Yet, the effect of comorbid conditions on the relationship between behavioral problems and ferritin level, indicating iron status, has not been investigated. Our results showed that subjects with comorbid ADHD had lower mean hemoglobin and MCV than subjects with pure ADHD. However, the frequency of iron deficiency or anemia was not higher in comorbid cases. When the whole

ADHD group was taken into account, CPRS and CTRS Total scores were negatively correlated with ferritin, showing that behavioral problems increase with lower iron stores. When this relationship was evaluated separetely for subjects with comorbid or pure ADHD, we found that the negative correlation of teacher ratings and ferritin was more prominent in the comorbid ADHD subjects. The relationship between parental ratings and ferritin was similar in each ADHD group. Regression analysis suggested that ferritin level might more significantly effect teacher reports. However, presence of comorbidity did not emerge as a significant factor in regression analysis. These results suggested that iron deficiency shows a complex relationship with the presence of comorbidity. Genetic mediators and gene-environment interactions are important in the understanding of persistence of ADHD symptoms and indvidual differences [24]. We did not investigate the effect of iron metabolism on the persistence of ADHD symptoms and the treatment response, but iron deficiency may be one of the environmental factors, like maternal smoking during pregnancy, low lead levels and premature birth [7], that must be taken into account when the effect of environment is investigated in future studies.

There were some limitations of the present study. The highly heterogenous nature of the comorbid group, including patients with externalization or internalization disorders was a clear limitation. Since there is no standard scale to measure the socioeconomic status, we could not evaluate this important variable. We could not evaluate age related changes in the symptomatolgy because of the cross-sectional design. This is important because ADHD is a developmental disorder and investigations with a broad age range might lead to masking of the population differences with developmental differences [25]. There were statistically significant difference of some hemoglobin between the groups, however, the clinical significance of this result is not very clear since the mean values were very close in the two groups. Another potential limitation was the multiple comparisons conducted, which might lead to Type 1 error. Considering these limitations, it must be kept in mind that the results are not definitive, but rather suggestive that there are some relationships that warrant further investigation.

Summary

Overall, these results suggested that lower ferritin level was associated with higher behavioral problems reported by both parents and teachers. However, when other factors, such as age, gender, MCV, hemoglobin, RDW, and comorbidity were taken into account, ferritin seemed to be a significant factor for behavior problems reported by the teachers. Subjects with comorbid ADHD had lower hemoglobin and MCV, which may contribute to behavioral problems. Presence of comorbid conditions might increase the effect of lower iron stores on behavioral measures. These results suggested that ferritin level must be evaluated in subjects with ADHD, particularly when comorbid conditions exists.

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Table 1

Comparison of Conners Parent and Teacher Rating Scales (CPRS, CTRS) scores and ferritin, hemoglobin, mean corpuscular volume (MCV) and reticulosite distribution width (RDW) levels in subjects with pure or comorbid ADHD. Analysis of variance

	Pure ADHD	Comorbid ADHD	F (1,147)	*P*
CPRS total score	33.3 ± 13.6	32.1 ± 14.1	.220	.639
CTRS total score	31.2 ± 10.4	30.4 ± 13.7	.137	.712
Ferritin	30.3 ± 14.3	33.1 ± 16.5	1.1	.296
Hemoglobin	13.9 ± .89	13.3 ± .88	12.1	.001
MCV	80.7 ± 4.6	78.8 ± 3.8	5.9	.016
RDW	14.6 ± 2.0	14.8 ± 2.0	.24	.623

Table 2

Results of linear regression analysis

Variables	CPRS total			CTRS total		
	B	***t***	***p***	***B***	***t***	***p***
Age	−.07	−.68	.50	−.22	−1.96	.052
Gender	−.13	−1.37	.17	−.14	−1.42	.16
Comorbidity	.03	.27	.79	.09	.87	.39
Ferritin	−.13	−1.29	.19	−.27	−2.80	.006
Hemoglobin	.26	2.25	.027	.20	1.79	.077
MCV	−.22	−2.02	.046	.13	1.19	.24
RDW	−.05	−.46	.65	−.16	−1.72	.089

Conners Parent Rating Scale (CPRS); Conners Teacher Rating Scale (CTRS); Mean Corpuscular Volume (MCV); Reticulosite Distribution Width (RDW)