Published in final edited form as:
Child Psychiatry Hum Dev. 2010 August ; 41(4): 441–447. doi:10.1007/s10578-010-0178-1.

Effects of Zinc and Ferritin Levels on Parent and Teacher Reported Symptom Scores in Attention Deficit Hyperactivity Disorder

Ozgur Oner,
Child Psychiatry Department, Dr Sami Ulus Children's Hospital, Telsizler, Altindag, Ankara, Turkey. Fogarty International Center Mental Health and Developmental Disabilities Program, Children's Hospital, Boston, MA, USA

Pinar Oner,
Child Psychiatry Department, Dr Sami Ulus Children's Hospital, Telsizler, Altindag, Ankara, Turkey

Ozlem Hekim Bozkurt,
Child Psychiatry Department, Diskapi Children's Hospital, Ankara, Turkey

Elif Odabas,
Child Psychiatry Department, Diskapi Children's Hospital, Ankara, Turkey

Nilufer Keser,
Child Psychiatry Department, Diskapi Children's Hospital, Ankara, Turkey

Hasan Karadag, and
Diskapi Yildirim Bayazit Training Hospital, Diskapi, Ankara, Turkey

Murat Kızılgün
Biochemistry Department, Diskapi Children's Hospital, Ankara, Turkey

Ozgur Oner: ozgur.oner@yahoo.com

Abstract

Objective—It has been suggested that both low iron and zinc levels might be associated with Attention Deficit Hyperactivity Disorder (ADHD) symptoms. However, the association of zinc and iron levels with ADHD symptoms has not been investigated at the same time in a single sample.

Method—118 subjects with ADHD (age = 7–14 years, mean = 9.8, median = 10) were included in the study. The relationship between age, gender, ferritin, zinc, hemoglobin, mean corpuscular volume and reticulosite distribution width and behavioral symptoms of children and adolescents with ADHD were investigated with multiple linear regression analysis.

Results—Results showed that subjects with lower zinc level had higher Conners Parent Rating Scale (CPRS) Total, Conduct Problems and Anxiety scores, indicating more severe problems. CPRS Hyperactivity score was associated both with zinc and ferritin levels. Conners Teacher Rating Scale (CTRS) scores were not significantly associated with zinc or ferritin levels.

Conclusions—Results indicated that both low zinc and ferritin levels were associated with higher hyperactivity symptoms. Zinc level was also associated with anxiety and conduct problems.

Correspondence to: Ozgur Oner, ozgur.oner@yahoo.com.

Since both zinc and iron are associated with dopamine metabolism, it can be speculated that low zinc and iron levels might be associated with more significant impairment in dopaminergic transmission in subjects with ADHD.

Keywords

ADHD; Zinc; Ferritin; Behavioral ratings

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, although several studies suggested that both genetic and environmental factor and their interactions are important. Some studies investigated the association of iron and zinc metabolisms with ADHD. A number of studies 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 reported by teachers or parents [2, 3 but also see 4]. Other studies have focused on the utility of iron supplementation in ADHD, with conflicting results [5, 6]. A relationship among iron deficit, restless legs syndrome (RLS) and other sleep disorders and ADHD has also been reported, suggesting a common dopaminergic impairment in these conditions [7, 8]. In our sample, we found that the rate of iron deficiency was significantly higher in ADHD subjects with RLS when compared with ADHD subjects without RLS, showing that depleted iron stores might increase the risk of having RLS in ADHD subjects. We also 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]. We also showed that in the ADHD group in general, parent and teacher ratings were significantly negatively correlated with ferritin level. When only pure ADHD subjects were taken into account, the correlations did not reach statistical signifance, suggesting that lower ferritin level was associated with higher behavioral problems reported by both parents and teachers. Presence of comorbid conditions might also increase the effect of lower iron stores on behavioral measures [9].

Several researchers reported a link between zinc levels and ADHD symptoms [reviewed in 10]. Results of other studies suggested that zinc supplementation might be effective in decreasing ADHD symptoms [11]. This makes sense since zinc is an inhibitor dopamine transporter, which is also the main target of stimulant medications [12]. An event related potentials study showed that zinc-deficient ADHD subjects might have different information processing when compared with non-zinc-deficient subjects [13].

However, the association of both iron and zinc metabolisms and ADHD symptoms in a single sample has not been investigated. This is important because both zinc and iron is important in dopamine pathway [12, 14]. In this study, our aim was to investigate the relationship between ferritin, zinc, hemoglobin, mean corpuscular volume (MCV) and reticulosite distribution width (RDW) and behavioral symptoms of children and adolescents with ADHD. We selected these hematological variables since iron deficiency is usually defined by low serum ferritin levels, or low MCV and high RDW values. Our hypothesis was that behavioral symptoms of subjects with ADHD were related to both ferritin and zinc levels.

Method

118 subjects with ADHD (97 boys (82.2%), 21 girls (17.8%); age 7–14 years, mean ± SD: 9.8 ± 2.3, median = 10) were included in the study. All of the cases were Caucasian. All subjects were recruited from the general outpatient clinic of a general hospital, who fulfilled the inclusion criteria [combined type ADHD diagnosis, being drug-naive, age 7–14; Conners Parent Rating Scale Hyperactivity score above cut-off (7)]. Informed consent was obtained from the parents before enrollment with local ethics committee approval for inclusion in the study. Diagnosis was based on DSM-IV criteria and made by the first author (Ozgur Oner), an experienced child psychiatrist using K-SADS-PL semi-structured interview. Informed consent process was verbal as is customary given the literacy level of the parents. 50 cases had comorbid oppositional defiant or conduct disorders, 32 cases had anxiety disorder or depression. All ADHD cases 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. All ADHD subjects were combined type since we excluded other subtypes. The parents could select to opt out of the study but none of the parents refused to participate Table 1.

Symptom severity was evaluated with Conners Parent and Teacher Rating Scales. The subjects who had scores lower than the proposed cut-off scores (CPRS Hyperactivity score = 7 and CTRS Hyperactivity score = 6) were excluded.

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 Turkish by Şener [18], and the Turkish form showed adequate validity and reliability (Cronbach's alpha .95).

Data Analysis

Multiple regression analysis was used in order to evaluate the effects of age, gender, ferritin, zinc, and hemoglobin levels, mean corpuscular volume and RDW values on the CPRS Learning Problems, Conduct Problems, Hyperactivity, Anxiety and Total scores as well as CTRS Hyperactivity, Conduct Problems, Inattentiveness and Total scores. 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. SPSS 13.0 statistical package was used for the analysis.

Results

CPRS Total score was significantly related with serum zinc level; cases with lower zinc level had higher scores, indicating more severe problems ($B = -.22$, $t = -2.4$, $p = .02$). CPRS Conduct Problems score was associated with zinc level ($B = -.20$, $t = -2.1$, $p = .04$) and also there was a statistical trend for higher scores in males ($B = -.18$, $t = -1.49$, $p = .055$). CPRS

Hyperactivity score was associated with zinc and ferritin ($B = -.26$, $t = -2.9$, $p = .005$ and $B = -.21$, $t = -2.3$, $p = .02$, respectively) levels and with being male ($B = -.18$, $t = -2.0$, $p = .048$). CPRS Anxiety score was associated with zinc level ($B = -.19$, $t = -2.0$, $p = .044$). CTRS Hyperactivity and Total scores were significantly associated with being male ($B = -.31$, $t = -3.1$, $p = .002$ and $B = -.22$, $t = -2.3$, $p = .02$, respectively) and RDW ($B = .27$, $t = 2.3$, $p = .03$ and $B = .28$, $t = 2.4$, $p = .02$, respectively).

Discussion

The results of the present study was consistent with previous studies, including our group's, showing that low ferritin level was associated with higher hyperactivity scores [2, 3]. However, in the present study we have found that low zinc level was also associated with high CPRS Hyperactivity score as well as high CPRS Anxiety, Conduct Problems and Total scores. That was also consistent with previous studies indicating higher scores in patients with low zinc levels [10]. This result expanded previous findings by showing that both iron and zinc metabolism were significantly associated with parental behavioral reports in a single sample. Our findings suggested that subjects with low zinc and low iron levels might have highest level of parent reported hyperactivity symptoms. Interestingly, neither ferritin nor zinc levels were associated with Learning Problems score, suggesting that they were more closely related with hyperactivity/impulsivity component of ADHD than inattention component. This was also consistent with our previous results [3]. We also found an association between RDW and teacher reported symptoms. High RDW is associated with iron deficiency, but it is not easy to interpret the results.

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 [14, 19, 20]. Zinc is a dopamine transporter inhibitor, since dopamine transporter is the main factor that determines the synaptic dopamine level, zinc level is supposed to be associated with dopaminergic transmission [12]. Neuroimaging, genetics, and animal studies have suggested that dopaminergic transmission is impaired in subjects with ADHD [21]. It can be speculated that iron and zinc deficiencies might cause further alterations in brain dopaminergic system, which seems to be already impaired in ADHD subjects [22]. Our results showed that both ferritin and zinc levels were negatively correlated with CPRS Hyperactivity score, suggesting an additive effect. On the other hand, only low zinc level was associated with CPRS Conduct Problems and Anxiety scores, suggesting that zinc and iron levels might be associated with different behaviors. It has recently been shown that zinc deficiency might induce depression-like behaviors in rats [23]. However, the link between internalization disorders and zinc deficiency is not very clear.

The most obvious limitation of the present study was the cross-sectional design. In cross-sectional studies one can not infer on causality, but can only report associations. The other potential limitation of the study was the clinical nature of the sample, these results may not be valid for population samples.

Summary

In summary, our results supported and extended previous findings by showing that there was a significant negative association between both zinc and ferritin levels and parent reported hyperactivity symptoms, suggesting that subjects with low levels of iron and zinc might be at increased risk of having higher levels of hyperactivity. Zinc level was also associated with parent reported conduct problems and anxiety.

Acknowledgments

Ozgur Oner, MD and Pinar Oner, MD are supported by Fogarty International Center Mental Health and Developmental Disabilities Program (D43TW05807) at Children's Hospital, Boston (Kerim Munir, PI).

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. IV. Washington DC: 1994.
2. Konofal E, Lecendreux M, Arnulf I, Mouren MC. Iron deficiency in children with attention deficit hyperactivity disorder. Arch Pediatr Adolesc Med. 2004; 158:1113–1115. [PubMed: 15583094]
3. Oner O, Alkar O, Oner P. Relation of ferritin levels with symptom ratings and cognitive performance in children with ADHD. Ped Int. 2008; 50:40–44.
4. Millichap JG, Yee MM, Davidson SI. Serum ferritin in children with attention-deficit hyperactivity disorder. Pediatr Neurol. 2006; 34:200–203. [PubMed: 16504789]
5. Sever Y, Ashkenazi A, Tyrano S, Weizman A. Iron treatment in children with attention deficit hyperactivity disorder. Neuropsychobiology. 1997; 35:178–180. [PubMed: 9246217]
6. Konofal E, Lecendreux M, Deron J, Marchand M, Cortese S, Zaïm M, Mouren MC, Arnulf I. Effects of iron supplementation on attention deficit hyperactivity disorder in children. Pediatr Neurol. 2008; 38:20–26. [PubMed: 18054688]
7. Oner P, Dirik EB, Taner Y, Caykoylu A, Anlar O. Association between low serum ferritin and restless legs syndrome in patients with attention deficit hyperactivity disorder. Tohoku J Exp Med. 2007; 213:269–276. [PubMed: 17984624]
8. Cortese S, Konofal E, Bernardina BD, Mouren MC, Lecendreux M. Sleep disturbances and serum ferritin levels in children with attention-deficit/hyperactivity disorder. Eur Child Adolesc Psychiatry. 2009; 18:393–399. [PubMed: 19205783]
9. Oner P, Oner O. Relationship of ferritin to symptom ratings children with attention deficit hyperactivity disorder, effect of comorbidity. Child Psychiatry Hum Dev. 2008; 39:323–330. [PubMed: 18165896]
10. Arnold LE, Bozzolo H, Hollway J, Cook A, DiSilvestro RA, Bozzolo DR, Crowl L, Ramadan Y, Williams C. Serum zinc correlates with parent- and teacher- rated inattention in children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2005; 15:628–636. [PubMed: 16190794]
11. Uçkardeş Y, Ozmert EN, Unal F, Yurdakök K. Effects of zinc supplementation on parent and teacher behaviour rating scores in low socioeconomic level Turkish primary school children. Acta Paediatr. 2009; 98:731–736. [PubMed: 19133873]
12. Krause J. SPECT and PET of the dopamine transporter in attention-deficit/hyperactivity disorder. Expert Rev Neurother. 2008; 8:611–625. [PubMed: 18416663]
13. Yorbik O, Ozdag MF, Olgun A, Senol MG, Bek S, Akman S. Potential effects of zinc on information processing in boys with attention deficit hyperactivity disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32:662–667. [PubMed: 18083281]
14. Erikson K, Pinero D, Connor J, Beard J. Iron status and distribution on iron in the brains of the developing rats. J Nutr. 1997; 127:2030–2038. [PubMed: 9311961]
15. Conners, CK. Conners' rating scales- revised. Multi-Health Systems Publishing; North Tonawada: 1997.
16. Dereboy, C.; Senol, S.; Sener, S. Adaptation of Conners' parent rating scale in Turkish. Proceedings 10th National Congress of Psychology; Ankara. 1998.
17. Goyette CH, Conners CK, Ulrich RF. Normative data on revised Conners' parent and teacher rating scales. J Abnorm Child Psychol. 1978; 6:221–236. [PubMed: 670589]
18. Sener S, Dereboy C, Dereboy IF, Sertcan Y. Conners' teacher rating scale Turkish version-I. Tr J Child Adolesc Ment Health. 1995; 2:131–141.
19. Wigglesworth, JM.; Baum, H. Iron dependent enzymes in the brain. In: Youdim, MBH., editor. Brain ıron: neurochemical and behavioral aspects. Taylor and Francis; New York: 1988. p. 25-66.

20. Ashkenazi R, Ben-Shachar D, Youdim MBH. Nutritional iron deficiency and dopamine binding sites in the rat brain. Pharmacol Biochem Behav. 1982; 17:43–47. [PubMed: 7184034]

21. Swanson JM, Kinsbourne M, Nigg J, Lanphear B, Stefanatos GA, Volkow N, Taylor E, Casey BJ, Castellanos FX, Wadwha PD. Etiological subtypes of attention deficit hyperactivity disorder: brain imaging, molecular genetics and environmental factors and the dopamine hypothesis. Neuropsychol Rev. 2007; 17:39–59. [PubMed: 17318414]

22. Volkow N, Wang J, Newcorn J, Telang F, Solanto MV, Fowler JS, Logan J, Ma Y, Schulz K, Pradhan K, Wong J, Swanson JM. Depressed dopamine activity in caudate and preliminary evidince of limbic involvement in adults with attention deficit hyperactivity disorder. Arch Gen Psychiatry. 2007; 64:932–940. [PubMed: 17679638]

23. Whittle N, Lubec G, Singewald N. Zinc deficiency induces enhanced depression-like behaviour and altered limbic activation reversed by antidepressant treatment in mice. Amino Acids. 2009; 36:147–158. [PubMed: 18975044]

Table 1

Multiple regression analysis results showing the *B*, *t* and *p* values for each dependent (Conners Parent or Teacher Rating Scale scores) varible with age, gender, ferritin, zinc, hemoglobin (Hb), mean corpuscular volume (MCV) and reticulosite distribution width (RDW) as independent factors

	Conners Parent Rating Scale			Conners Teacher Rating Scale				
	Total *B; t; p*	**Conduct problems *B; t; p***	**Learning problems *B; t; p***	**Hyperactivity *B; t; p***	**Hyperactivity *B; t; p***	**Inattention B; t; p**	**Conduct problems *B; t; p***	**Total *B; t; p***
Age	.11; 1.1; .28	.01; .06; .95	.18; 1.8; .08	−.02; −.17; .87	−.07; −.65; .52	.08; .72; .47	−.01; −.11; .91	.0; .0; .98
Gender	−.04; −.50; .62	−.18; −1.9; .06	−.04; −.41; .68	−1.8; −2.0; .048	−.31; −3.1; .002	−.05; −.44; .66	−.19; −1.8; .07	−.22; −2.2; .03
Zinc	−.22; −2.3; .02	−.20; −2.1; .04	−1.0; −.98; .32	−.26; −2.9; .005	−.01; −.05; .96	.08; .72; .47	.13; 1.3; .20	.08; .79; .43
Hb	.02; .14; .89	.05; .44; .66	.08; .67; .51	.09; .84; .41	.04; .30; .77	−.07; −.55; .58	−.08; −.67; .50	−.05; −.37; .71
MCV	.08; .71; .48	.16; 1.4; .17	−.08; −.71; .48	.17; 1.5; .13	.08; .68; .50	.18; 1.4; .17	.16; 1.3; .19	.17; 1.4; .17
RDW	.04; .32; .75	.08; .69; .49	.04; .37; .71	.20; 1.9; .06	.27; 2.3; .02	.19; 1.6; .12	.23; 1.9; .06	.28; 2.4; .02
Ferritin	−.16; −1.6; .10	−.11; −1.2; .25	.01; .12; .91	−.21; −2.3; .02	.08; .84; .40	−.16; −1.5; .14	−.02; −.20; .85	−.03; −.33; .74