DOI: 10.5455/bcp.20120403015900

Effect of Ferritin on Short-Term Treatment Response in Attention Deficit Hyperactivity Disorder

Pinar Oner[1,3], Ozgur Oner[1,3], Esra Cop[2], Kerim M. Munir[4,5]

ÖZET:

Ferritinin dikkat eksikliği hiperaktivite bozukluğunda kısa süreli tedaviye cevap üzerine etkisi

Amaç: Birçok çalışmada, demir eksikliği ve ferritin düzeyinin öğretmen ve ebeveyn dikkat eksikliği hiperaktivite bozukluğu (DEHB) puanları ile ilişkili olduğu gösterilmiştir. Sonuçlar çelişkili olsa da demir takviyesinin DEHB belirtilerini azalttığı bildirilmiştir. Tüm bu çalışmalar göz önünde bulundurulduğunda demir eksikliği ve ferritin düzeyinin DEHB'nin stimülanlar ile rutin farmakolojik tedavisine etkisini araştıran büyük ölçekli bir çalışma klinik bakış açısından konuya açıklık getirecektir.

Yöntem: DEHB bileşik ya da hiperaktivite-impulsivite ön planda alt tipleri olan 345 denek çalışmaya dahil edilmiştir. Tüm tanılar, DSM-IV ölçütlerine göre ve Çocuk ve Gençler için Duygulanım Bozukluğu ve Şizofreni Ölçeği-Şimdi ve Yaşam boyu Versiyonu (ÇGDBŞÖ-ŞY) yarı yapılandırılmış görüşme tekniği kullanılarak yazarlar tarafından yapılmış direkt görüşmelerle koyulmuştur. Tedaviye yanıt kriterleri: 1) Conners Anne-Baba Derecelendirme Ölçeği (CADÖ) ve Conners Öğretmen Derecelendirme Ölçeği (CÖDÖ) tedavi öncesi Hiperaktivite (HA) ve Toplam sorunlar puanlarında %25 ya da daha fazla azalma; 2) hem CADÖ hem de CÖDÖ puanlarının eşiğin altında olması (çok düzeldi).

Bulgular: Çalışmaya katılanların 255'i (%73.9) OROS-metilfenidat (OROS-MPH), 90 hasta kısa salınımlı metilfenidat (IR-MPH) tedavisi aldı. Ortalama±sd OROS-MPH ve IR-MPH dozları sırasıyla 28.8±8.1 ve 20.9±7.1 mg'dı. Çalışmaya katılanların %52.5'i tedavi başlanmadan önce hiç ilaç kullanmamıştı. 278 (%80.6) denek bileşik tip DEHB, diğerleri hiperaktivite-dürtüsellik ön planda DEHB tanıları aldı. Çalışmaya katılanların 60'ında (17.4%) komorbid bozukluk yokken %38.3'ünde bir komorbid bozukluk, %32.8'inde iki komorbid bozukluk ve %11.6'sında üç ya da daha fazla komorbid bozukluk vardı. En sık görülen komorbid bozukluk Karşıt Olma Karşı Gelme Bozukluğu/ Davranım Bozukluğu (KOKGB/DB, %51.6) iken, bunu sırasıyla Öğrenme Güçlüğü (ÖG, %35.4) ve Anksiyete Bozuklukları (AB, %15.9) izledi. Lojistik regresyon analizine göre komorbid KOKGB/DB ve ÖG olan olguların tedaviye daha az yanıt verdiği gözlendi. Sonuçlar ile ferritin düzeyi ve demir eksikliği arasında istatistiksel olarak anlamlı bir ilişki bulunmadı.

Sonuç: Bileşik ya da hiperaktivite-dürtüsellik ön planda alt tipleri olan DEHB'li deneklerden oluşan büyük bir grupta bir çok etkeni kontrol ettikten sonra ne demir eksikliği (ferritin<12 ng/ml) ne de ferritin düzeyinin stimülanlarla kısa süreli tedavi sonuçlarıyla ilişkili olmadığı bulundu. Komorbid KOKGB/DB ve ÖÖG olan hastalarda CÖDÖ toplam puanında %25 ya da daha fazla azalma yoktu. Komorbid KOKGB/DB olması ayrıca CADÖ toplam ve HA puanlarına bakıldığında tedaviye yanıtta negatif yordayıcıydı. Demir eksikliği olan DEHB'li deneklerde negatif tedavi yanıtının olmaması ve ferritin düzeyi ile tedavi yanıtı arasında negatif ilişki saptanmaması, demir metabolizması ve çok heterojen bir bozukluk olan DEHB arasındaki ilişkinin inanıldığının aksine daha karmaşık olduğunu ortaya koymaktadır.

Anahtar sözcükler: Dikkat eksikliği hiperaktivite bozukluğu, ferritin, farmakolojik tedavi, metilfenidat

Klinik Psikofarmakoloji Bülteni 2012;22(4):325-31

ABSTRACT:

Effect of ferritin on short-term treatment response in attention deficit hyperactivity disorder

Objectives: Several studies have shown that iron deficiency and ferritin levels are associated with parent and teacher Attention Deficit Hyperactivity Disorder (ADHD) ratings. Although there are conflicting results, it has also been reported that iron supplementation may help to decrease ADHD symptoms. When all these previous studies are taken into account, it is clear that a large study investigating the effects of iron deficiency and ferritin levels on routine pharmacological treatment of ADHD with stimulants would be helpful to elucidate this treatment from a clinical point of view.

Methods: A total of 345 subjects with combined or predominantly hyperactive-impulsive (PHI) subtypes of ADHD were included. All diagnoses were based on the DSM-IV criteria and ascertained by direct interviews conducted by the authors, who are experienced child psychiatrists certified in the use of the Schedule for Affective Disorders and Schizophrenia for School-Age Children — Present and Lifetime Version (K-SADS-PL) semi-structured interview. The two treatment response criteria were: 1) 25% or more decrease in pre-treatment Conners Parent Rating Scale (CPRS) and Conners Teacher Rating Scale (CTRS) Hyperactivity (HA) and Total Problems scores; 2) CPRS and CTRS HA scores lower than the cut-off point ("very improved").

Results: A total of 255 (73.9%) patients were on OROS-methylphenidate (OROS-MPH) and 90 (26.1%) were on immediate release methylphenidate (IR-MPH). The mean±sd of OROS-MPH and IR-MPH doses were 28.8±8.1 and 20.9±7.1 mg, respectively. More than half (52.5%) of the subjects were previously drug-naive at treatment inception. Two hundred and seventy eight (80.6%) subjects had combined subtype ADHD and the remainder had predominantly hyperactive-impulsive subtype. Only 60 (17.4%) of the subjects had no comorbid disorders, while 38.3% had one comorbid disorder, 32.8% had two comorbid disorders, and 11.6% had three or more comorbid disorders. The most frequent comorbidity was Oppositional Defiant Disorder/Conduct Disorder (ODD/CD, 51.6%), followed by Learning Disabilities (LD, 35.4%) and Anxiety Disorders (AD, 15.9%). Logistic regression analysis showed that subjects with comorbid ODD/CD and LD were less likely to respond to treatment. Ferritin levels and iron deficiency were not associated significantly with outcomes.

Conclusions: In a large sample of subjects with combined or predominantly hyperactive-impulsive subtypes of ADHD, after controlling for several factors, we found that neither iron deficiency (ferritin <12 ng/ml) nor ferritin levels were associated with less favorable short-term treatment outcomes with stimulants. Subjects with comorbid ODD/CD and LD were less likely to have a 25% or more decrease in CTRS Total score. The presence of ODD/CD was also a negative predictor of treatment response in terms of CPRS Total and HA scores. The lack of a negative treatment response in ADHD subjects with iron deficiency and lack of a negative association with ferritin levels suggest that the relationship between iron metabolism and ADHD, a highly heterogeneous disorder, may be more complicated than previously believed.

Key words: Attention deficit hyperactivity disorder, ferritin, pharmacologic therapy, methylphenidate

Bulletin of Clinical Psychopharmacology 2012;22(4):325-31

[1]MD, Associate Professor, Department of Child and Adolescent Psychiatry, Dr. Sami Ulus Childrens' Hospital, Ankara - Turkey
[2]MD, Department of Child and Adolescent Psychiatry, Dr. Sami Ulus Childrens' Hospital, Ankara - Turkey
[3]MD, Associate Professor, Fogarty International Center Mental Health and Developmental Disabilities Program, Children's Hospital, Boston, MA, USA
[4]MD, MPH, DSc, Fogarty International Center Mental Health and Developmental Disabilities Program, Children's Hospital, Boston, MA, USA
[5]MD, MPH, DSc, Children's Hospital, Boston; Harvard Medical School, Department of Psychiatry, Boston, MA, USA

Yazışma Adresi / Address reprint requests to: Pinar Oner, MD, Dr. Sami Ulus Children's Hospital, Child Psychiatry Department, Yenimahalle Devlet Hastanesi, Batıkent, Ankara - Turkey

Telefon / Phone: +90-312-305-6533

Faks / Fax: +90-312-305-6528

Elektronik posta adresi / E-mail address: pinaryoner@yahoo.com

Gönderme tarihi / Date of submission: 20 Mayıs 2011 / May 20, 2011

Kabul tarihi / Date of acceptance: 3 Nisan 2012 / April 3, 2012

Bağıntı beyanı:
P.O., O.O., E.C., K.M.M.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:
P.O., O.O., E.C., K.M.M.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most common pediatric psychiatric disorders. The disorder is characterized by a triad of inattention, impulsivity, and hyperactivity symptoms, as well as alterations in executive functioning. The etiology of ADHD is not clear, but several lines of evidence imply that dopaminergic neurotransmission is impaired in ADHD (1). Stimulants, including methylphenidate (MPH), which are the most effective treatment for ADHD, affect dopamine. Iron is a co-factor of tyrosine hydroxylase, which is the rate-limiting enzyme in dopamine synthesis (2).

Several studies have shown that iron deficiency and ferritin levels are associated with parent and teacher ADHD ratings (3-6, but also see 7,8). Although there are conflicting results, it has also been reported that iron supplementation may help to decrease ADHD symptoms (9,10). Iron deficiency is also important in Restless Leg Syndrome (RLS) (11), which is also treated by dopaminergic agents. We have shown in previous studies that iron deficiency might be associated both with ADHD and RLS (4).

When all these previous studies are taken into account, it is clear that a large study investigating the effects of iron deficiency and ferritin levels on routine pharmacological treatment of ADHD with stimulants would be helpful to elucidate the effectiveness of this treatment from a clinical point of view. In the present study, our aim was to fill this important gap in the literature. It has been shown that comorbid disorders and ADHD subtypes might be predictors of treatment response (12,13), therefore we controlled these factors along with age, gender, and baseline parent and teacher ratings. We excluded subjects with predominantly inattentive subtype ADHD for two reasons. First, previous studies have shown that ferritin level was associated with hyperactivity, but not attention problem ratings (4,6). Ferritin level was also not associated with cognitive test scores (6). Second, while subjects with ADHD hyperactive-impulsive subtype were shown to be very similar to the combined group and that it can be viewed as a milder form of the combined subtype [14], several differences between the combined subtype and inattentive subtypes have been described, which might include treatment response. As we aimed to reflect daily clinical practice, we included all preparations of MPH available in Turkey. Therefore, patients who were on either immediate release (IR-MPH) or OROS-methylphenidate (OROS-MPH) have been included. Several studies have shown that OROS-MPH is as effective (15), or even more effective (16), than IR-MPH. The purpose of the present study was to investigate whether ferritin level had an impact on stimulant treatment response, when other important factors were controlled.

METHODS

Patient Population

Three-hundred and fortyfive subjects with ADHD were included in the study (302 males, 87.5%, ages 6-15, mean: 9.1 years, standard deviation: 2.1 years). All of the cases were Caucasian. All subjects were recruited from consecutive referrals to an outpatient clinic of a general hospital and fulfilled the inclusion criteria for ADHD combined or predominantly hyperactive-impulsive (PHI) subtype diagnoses per the DSM-IV criteria, being drug free at least for 15 days, and 6-15 years of age. We excluded the patients who were on medication, who had ADHD predominantly inattentive subtype, who had parent or teacher hyperactivity ratings below the proposed cut-offs, and whose parents or teachers did not complete the rating scales.

Study Design

All diagnoses was based on DSM-IV criteria and were ascertained by direct examinations (P.O, O.O, E.C) conducted by the authors, who are experienced child psychiatrists certified in the use of the Schedule for Affective Disorders and Schizophrenia for School-Age Children — Present and Lifetime Version (K-SADS-PL) semi-structured interview, validated in Turkish (17,18). The informed consent process was verbal as is customary given the literacy level of the parents and the parents were informed that the clinical data may be used for scientific purposes. Institutional ethical committee approval was obtained for the study. All index subjects with ADHD had an unremarkable medical history (other than ADHD) and were assessed for anxiety disorder, mood disorder, oppositional defiant disorder/conduct disorder, as well as tics and elimination disorders with the corresponding K-SADS-PL modules. Learning disabilities were evaluated with the Wechsler Intelligence Scale for Children- Revised

(WISC-R) including the reading, writing, and mathematics tasks. All assessments were done as a part of a routine clinical work up for the patients seen in the clinic. The parents had the option to opt out of the study, but none of the parents refused to participate.

Symptom severity was evaluated with the Conners Parent and Teacher Rating scales. Conners Parent Rating Scale (CPRS). This form includes 48 items, and aims to evaluate the behavior of children assessed by their parents (19). The scale includes oppositional behavior, inattentiveness, hyperactivity, psychosomatic, and irritability domains. The Turkish translation has been demonstrated to have good validity and reliability (20). The proposed hyperactivity (HA) score cut-off is 8.

Conners Teacher Rating Form (CTRS). This form includes 28 items, and aims to rate classroom behavior of children assessed by teachers (21). There are three subscales: 8 items for inattentiveness, 7 items for hyperactivity and 8 items for conduct problems. The CTRS has been translated into Turkish by Şener (22), and the Turkish form showed adequate validity and reliability (Cronbach's alpha .95). The proposed HA score cut-off is 7.

There were two treatment response criteria. First, treatment response was defined as a 25% or more decrease from pre-treatment CPRS and CTRS HA and Total Problems scores. Second, we defined subjects with both CPRS and CTRS HA scores below the cut-off as "very improved." We selected HA scores in particular since we found in different samples that ferritin level and iron deficiency was more closely associated with HA scores rather than attention problem scores. We also took both teacher and parent ratings into account since those may measure different behaviors.

Since satiety effects iron level and ferritin level changes with acute infections, fasting blood was drawn from each patient. Blood was drawn from patients with acute infections at least 15 days after the infection with the control of clinical signs and symptoms and sedimentation rate. The serum ferritin was measured by a solid-phase, 2-site chemiluminescent immunometric assay (Immulite 2000™; Diagnostic Products®, Los Angeles, CA).

Statistics

Baseline and one-month parent and teacher ratings were compared using the paired-samples t-test. Logistic regression analyses were computed in order to calculate the effects of gender, age, ADHD subtype (combined, predominantly hyperactive-impulsive), comorbid anxiety disorders (AD), learning disabilities (LD), oppositional defiant disorder/conduct disorder (ODD/CD), ferritin level, medication (OROS-MPH and IR-MPH), and corresponding baseline CPRS and CTRS scores, on treatment response (defined as a 25% more decrease from baseline score). We also defined subjects with both CPRS and CTRS HA scores below cut-off scores (<7 for CPRS and <8 for CTRS) as "very improved." The analysis was repeated with CPRS and CTRS HA and Total Problems scores as outcomes, separately. P<0.05 was reported as statistically significant. SPSS 13.0 was used for the analysis.

RESULTS

There were 302 boys (87.5%) and 43 girls in the study. The age range was 6 to 15 years with a mean of 9.1 and standard deviation (sd) of 2.1 years. Two hundred and fifty five (73.9%) patients were on OROS-MPH and 90 were on IR-MPH. The mean±sd OROS-MPH and IR-MPH doses were 28.8±8.1 and 20.9±7.1 mg, respectively. More than half of the subjects (52.5%) were previously drug-naive at treatment inception. Most subjects (278, 80.6%) had combined subtype ADHD and the remainder had predominantly hyperactive-impulsive subtype. Sixty (17.4%) of the subjects had no comorbid disorders, while 38.3% had one comorbid disorder, 32.8% had two comorbid disorders, and 11.6% had three or more comorbid disorders. The most frequent comorbidity was ODD/CD (51.6%), followed by LD (35.4%) and AD (15.9%). About 7.5% of the subjects had a ferritin level <12 ng/ml.

Baseline and post-treatment rating scores are summarized in Table 1. All rating scores decreased significantly with treatment. The percentage of subjects who had a 25% or more decrease from pretreatment scores

Table 1: Baseline and post-treatment rating scores and paired-samples t-test scores.

	Baselined	Post-treatment[§]	t[‖]
CTRS* HA[†]	11.0±3.6	8.7±3.6	11.0
Total	32.6±9.4	26.4±9.5	6.1
CPRS[‡] HA	8.5±2.8	7.1±3.0	10.9
Total	29.3±11.4	24.4±10.8	8.0

[‖]All p<0.001.
*Conners Teacher Rating Scale, [‡]Conners Parent Rating Scale,
[†]Hyperactivity, [§]mean±standard deviation

Table 2: Logisic regression results

	Dependent Variables											
	CPRS Total 25% Change		CPRS Hyperactivity 25% Change		CTRS Total 25% Change		CTRS Hyperactivity 25% Change		CPRS Hyperactivity <7		CTRS Hyperactivity <8	
Independent Variables	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Gender	0.72	0.34-1.5	1.1	0.51-2.2	1.5	0.69-3.2	0.80	0.37-1.7	1.3	0.60-2.6	1.7	0.78-3.8
Age	0.95	0.85-1.1	1.1	0.97-1.2	1.0	0.90-1.1	0.98	0.87-1.1	1.0	0.92-1.2	1.0	0.87-1.1
Ferritin	1.0	0.99-1.1	0.98	0.97-1.0	1.0	0.99-1.0	1.2	0.87-1.6	1.0	0.98-1.1	1.0	0.98-1.0
Subtype	1.2	0.87-1.6	1.3	0.94-1.7	1.2	0.90-1.6	1.6	0.80-3.2	1.4*	1.03-1.9	1.0	0.72-1.4
Anxiety	0.67	0,32-1. 4	0.4	0.47-1.9	0.92	0.43-1.9	0.65	0.39-1.1	0.78	0.40-1.5	1.6	0.77-3.2
LD	0.75	0.44-1.3	0.80	0.48-1.3	0.44*	0.26-0.77	0.68	0.43-1.1	0.70	0.41-1.2	0.65	0.37-1.1
ODD/CD	0.53**	0.32-0.87	0.50*	0.30-0.80	0.47*	0.29-0.78	1.3	0.74-2.2	0.54**	0.32-0.87	0.70	0.41-1.2
Drug	0.85	0.49-1.5	0.78	0.45-1.4	1.0	0.58-1.9	1.0	0.99-1.0	0.80	0.45-1.4	1.0	0.65-2.2
Baseline score	1.07*	1.04-1.1	1.3*	1.14-1.4	1.1*	1.02-1.1	1.1*	1.04-1.2	0.80*	0.73-0.88	0.78*	0.71-0.84

CPRS: Conners Parent Rating Scale, CTRS: Conners Teacher Rating Scale, CI: Confidence Interval, LD: Learning Disorder, ODD/CD: Oppositional Defiant Disorder/Conduct Disorder. *p<0.01, **p<0.05.

were as follows: CTRS HA: 41.7%; Total: 37.6%; CPRS HA: 39.0%; Total: 39.2%.

The ferritin level was significantly negatively correlated with the baseline CPRS HA score (r=-0.12, p=0.03).

The logistic regression analyses (Table 2) indicated that subjects with comorbid ODD/CD (B=0.47, p=0.006) and LD (B=0.44, p=0.004) were less likely to have a 25% or more decrease in CTRS Total score. The presence of ODD/CD was also a negative predictor of treatment response in terms of CPRS Total (B=0.53, p=0.012) and HA scores (B=0.50, p=0.003). Baseline CPRS and CTRS scores were significantly associated with treatment response, indicating that subjects with higher baseline scores were more likely to have a 25% or higher decrease after treatment.

Only 56 (15.5%) of the subjects were "very improved,", meaning that they have below cut-off HA scores on both the CPRS and CTRS after treatment. Ferritin level or the presence of iron deficiency was not associated significantly with this outcome. Subjects with ODD/CD comorbidity who had higher scores before the treatment had a lower chance of being "very improved". Age, gender, ADHD subytpe (Combined vs PHI), and drug (OROS-MPH vs IR-MPH) were not significantly associated with treatment response.

DISCUSSION

In a large sample of subjects with ADHD combined or PHI subtypes, after controlling for several factors, we found that both iron deficiency (ferritin <12 ng/ml) or ferritin level were not associated with less favorable short-term treatment outcome with stimulants. Consistent with previous studies (4,6), the parent hyperactivity score was negatively associated with ferritin level, meaning that subjects with lower ferritin levels had higher pre-treatment parent reported hyperactivity. Baseline rating scores were also positively associated with a 25% or more decrease with treatment. This raises the possibility that more favorable treatment response in terms of change in parent ratings might be due to regression to the mean effect. This implies that subjects with the highest baseline scores have a higher chance of reduced post-treatment scores. It must be kept in mind that a 25% decrease from baseline scores does not necessarily mean total improvement. Owens and associates have reported that severe cases tend to show a large treatment response although they are less likely to be normalized by treatment (23). In fact, being in the "very improved" group, defined as having below cut-off level hyperactivity scores in both parent and teacher ratings, was not correlated with ferritin level or associated with iron deficiency (ferritin <12 ng/ml).

Although previous studies have shown that ODD/CD was not a significant moderator of treatment (12,24), in our study subjects with comorbid ODD/CD and LD showed a less favorable response to the treatment. Particularly the negative effect of ODD/CD on treatment response was seen in both parent and teacher ratings and it was also reflected in the "very improved" group. These

results suggested that at least in the short-term, for these children combined medication and psychosocial interventions might be necessary. In fact, previous studies have reported that combined medication and behavioral treatments might lead to better results in decreasing oppositonal/aggressive symptoms and better academic functioning (25).

Age and gender were not important predictors, as have also been previously reported (12). There were no significant differences between OROS-MPH and IR-MPH. This was consistent with some (15), but not all (see 16) of the previous studies. However, it must be kept in mind that the present study was not a controlled clinical trial aiming to compare the efficacy of the two preparations.

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 (26-28). Neuroimaging, genetics, and animal studies have suggested that dopaminergic transmission is impaired in subjects with ADHD (29). Functional neuroimaging studies have shown that stimulants increase striatal and cortical extracellular dopamine levels (30). Therefore, it was reasonable to hypothesize that iron deficiency and ferritin levels would be associated with a decreased response to stimulant treatment. However, our findings did not support this in our clinical sample. Neuroimaging studies can provide data, about whether or not iron deficiency alters stimulant actions in brain. It would also be interesting to investigate whether tyrosine hydroxylase genotype moderates the association of iron metabolism and ADHD symptoms and treatment response.

Investigating the association between iron metabolism and ADHD by using different methodologies may further help our understanding of both conditions. However, the correlation between ferritin level and ADHD symptoms is not very strong, and it is more evident in parent ratings (6). It is not associated significantly with cognitive measures (4). The lack of a negative treatment response in ADHD subjects with iron deficiency and the lack of a negative association with ferritin levels suggest that the relationship between iron metabolism and ADHD, a highly heterogeneous disorder, may be more complicated than previously believed. Based on our study, it may be premature to assume that iron deficiency and ferritin levels are not important in defining treatment response to stimulants. At the outset of the dopamine hypothesis for ADHD it was postulated that executive functioning in index subjects, in addition to ADHD symptoms, is also modulated by dopaminergic pathways. Further, during childhood, low ferritin levels per se may have a more overarching effect on the development of the central nervous system, leading not only to correlation with high HA symptoms in ADHD but a range of neurobehavioral outcomes (including RLS) that are not necessarily captured by our current DSM definitions. It is of interest that although ferritin was not significantly correlated with cognitive measures in our study, nevertheless, there was a lack of treatment response in subjects with ODD/CD and LD, representing the first and second largest comorbidity subgroups, with greater likelihood of CNS and executive function problems, as well as lack of response to psychopharmacological treatment, as has been supported by previous studies. The lack of stimulant response and need for combined remedies for these children do not also necessarily imply a psychosocial etiology for these comorbidity subgroups, that tend to be widely heterogeneous in their respective etiologies. Further studies are needed in younger children with neurobehavioral and cognitive subtypes of ADHD to elucidate neuropsychological predictors of treatment response to stimulants and iron metabolism.

There were some limitations of the present study. First of all, this was a naturalistic study and there were no placebo control or randomization. Second, treatment response depends on the definition and although we used two different definitions the results could have been different with another type of definition. Third, treatment response could change over time and the results could be different with long-term follow-up.

CONCLUSIONS

In a large sample of subjects with combined or PHI subtypes of ADHD, after controlling for several factors, we found that neither iron deficiency (ferritin <12 ng/ml) nor ferritin level were associated with less favorable short-term treatment outcomes with stimulants. We investigated whether ferritin level and iron deficiency (ferritin<12 ng/ml) affects treatment response to stimulants (IR-MPH or OROS-MPH). Logistic regression analyses were computed in order to calculate the effects

of gender, age, ADHD subtype, comorbid anxiety disorders (AD), learning disabilities (LD), oppositional defiant/conduct (ODD/CD) disorders, ferritin level, and medication (OROS-MPH and IR-MPH) response. Ferritin level was significantly negatively correlated with the baseline CPRS HA score. Subjects with comorbid ODD/CD and LD were less likely to have a 25% or more decrease in the CTRS Total score. The presence of ODD/CD was also a negative predictor of treatment response in terms of the CPRS Total and HA scores. Ferritin level and iron deficiency were not associated significantly with the 25% or more decrease in initial score or the "very improved" outcome. The lack of a negative treatment response in ADHD subjects with iron deficiency and the lack of a negative association with ferritin levels suggest that the relationship between iron metabolism and ADHD, a highly heterogeneous disorder, may be more complicated than previously believed.

References:

1. Swanson JM, Kinsbourne M, Nigg J, Lanphear B, Stefanatos GA, Volkow N, et al. Etiological subtypes of attention deficit hyperactivity disorder: brain imaging, molecular genetics and environmental factors and the dopamine hypothesis. Neuropsychol Rev 2007;17(1):39-59.
2. Youdim MB. Brain iron deficiency and excess; cognitive impairment and neurodegeneration with involvement of striatum and hippocampus. Neurotox Res 2008;14(1):45-56.
3. Konofal E, Lecendreux M, Arnulf I, Mouren MC. Iron deficiency in children with attention deficit hyperactivity disorder. Arch Pediatr Adolesc 2004;158(12):1113-5.
4. Oner O, Alkar O, Oner P. Relation of ferritin levels with symptom ratings and cognitive performance in children with ADHD. Pediatr Int 2008;50(1):40-4.
5. Juneja M, Jain R, Singh V, Mallika V. Iron deficiency in Indian children with attention deficit hyperactivity disorder. Indian Pediatr 2010;47(11):955-8.
6. Oner O, Oner P, Bozkurt OH, Odabas E, Keser N, Karadag H, et al. Effects of zinc and ferritin levels on parent and teacher reported symptom scores in attention deficit hyperactivity disorder. Child Psychiatry Hum Dev 2010;41(4):441-7.
7. Millichap JG, Yee MM, Davidson SI. Serum ferritin in children with attention-deficit hyperactivity disorder. Pediatr Neurol 2006;34(3):200-3.
8. 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 Jun 2010;32(2):132-8.
9. Sever Y, Ashkenazi A, Tyrano S, Weizman A. Iron treatment in children with attention deficit hyperactivity disorder. Neuropsychobiology 1997;35(4):178-80.
10. 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.
11. 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(7):393-9.
12. Hinshaw SP. Moderators and mediators of treatment outcome for youth with ADHD: understanding for whom and how interventions work. Ambul Pediatr 2007;7(Suppl.1):S91-S100.
13. Stein M, Sarampote CS, Waldman ID, Robb AS, Conlon C, Pearl PL, et al. A dose-response study of OROS methylphenidate in children with attention-deficit hyperactivity disorder. Pediatrics 2003;112(5):404.
14. Lahey BB, Pelham WE, Loney J, Lee SS, Willcutt E. Instability of the DSM-IV subtypes of ADHD from preschool through elementary school. Arch Gen Psychiatry 2005;62(8):896-902.
15. Wolraich ML, Greenhill LL, Pelham W, Swanson J, Wilens T, Palumbo D, et al. Randomized, controlled trial of OROS methylphenidate once a day in children with attention deficit/hyperactivity disorder. Pediatrics 2001;108(4):883-92.
16. Steele M, Weiss M, Swanson J, Wang J, Prinzo RS, Binder CE. A randomized, controlled, effectiveness trial of oros-methylphenidate compared to usual care with immediate-release methylphenidate in attention deficit- hyperactivity disorder. Can J Clin Pharmacol 2006;13(1):50-62.
17. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36(7):980-8.
18. Gökler B, Ünal F, Pehlivantürk B, Çengel Kültür SE, Akdemir D, Taner Y. Validity and reliability of the Turkish form of schedule of affective disorders and schizophrenia for school age children, present and life-time version (K-SADS-PL). Çocuk ve Gençlik Ruh Sağlığı Dergisi-Turkish Journal of Child and Adolescent Mental Health 2004;11(3):109-16. (Turkish).
19. Conners CK. Conners' Rating Scales- Revised. North Tonawada, NY: Multi-Health Systems Publishing, 1997.
20. Dereboy C, Senol S, Sener S. Adaptation of Conners' parent rating scale in Turkish. In: Proceedings 10th National Congress of Psychology. Ankara: 1998.
21. Goyette CH, Conners CK, Ulrich RF. Normative data on revised Conners' parent and teacher rating scales. J Abnorm Child Psychol 1978;6(2):221-36.
22. Sener S, Dereboy C, Dereboy IF, Sertcan Y. Conners' Teacher Rating Scale Turkish version-I. Çocuk ve Gençlik Ruh Sağlığı Dergisi-Turkish Journal of Child and Adolescent Mental Health 1995;2(3):131-41. (Turkish).
23. Owens EB, Hinshaw SP, Kraemer HC, Arnold LE, Abikoff HB, Cantwell DP, et al. Which treatment for whom for ADHD? Moderators of treatment response in the MTA. J Consult Clin Psychol 2003;71(3):540-52.

24. Moderators and mediators of treatment response for children with attention-deficit/hyperactivity disorder: The multimodal treatment study of children with attentiondeficit/ hyperactivity disorder. Arch Gen Psychiatry 1999;56(12):1088-96.

25. Jensen PS, Hinshaw SP, Swanson JM, Greenhill LL, Conners CK, Arnold LE, et al. Findings from the NIMH multimodal treatment study of ADHD (MTA): implications and applications for primary care providers. J Dev Behav Pediatrics 2001;22(1):60-73.

26. Barkley RA. Comorbid disorders, adjustment, and subtyping. In Attention Deficit Hypeactivity Disorder: A Handbook for Diagnosis and Treatment. New York: Guilford Press Press; 2006. p. 184-219.

27. Wigglesworth JM, Baum H. Iron dependent enzymes in the brain. In: Youdim MBH (editor). Brain Iron:Neurochemical and Behavioral Aspects. New York: Taylor and Francis;1988. P. 25-66.

28. Ashkenazi R, Ben-Shachar D, Youdim MBH. Nutritional iron deficiency and dopamine binding sites in the rat brain. Pharmacol Biochem Behav 1982;17(Suppl. 1):S43-S7.

29. Swanson JM, Kinsbourne M, Nigg J, Lanphear B, Stefanatos GA, Volkow N, et al. Etiological subtypes of attention deficit hyperactivity disorder: brain imaging, molecular genetics and environmental factors and the dopamine hypothesis. Neuropsychol Rev 2007;17(1):39-59.

30. Carboni E, Silvagni A. Experimental investigations on dopamine transmission can provide clues on the mechanism of the therapeutic effect of amphetamine and methylphenidate in ADHD. Neural Plast 2004;11(1/2):77-95.