Iron Deficiency in Pediatric Patients in Long-Term Risperidone Treatment

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Abstract

Objective: Atypical antipsychotics, increasingly used in children and adolescents, modulate brain dopamine. Iron plays a critical role in dopaminergic signaling. Therefore, we explored whether body iron status is related to psychiatric symptom severity, treatment response, and tolerability following extended antipsychotic therapy.

Methods: Between November 2005 and August 2009, medically healthy 7–17-year-old risperidone-treated participants enrolled in a cross-sectional study examining the long-term safety of this antipsychotic. Anthropometric measurements were obtained. Psychiatric symptom severity and dietary intake were assessed. Serum ferritin, transferrin receptor, and prolactin concentrations were measured. Linear multivariable regression analysis tested the association among body iron, symptom severity, the dose of risperidone and psychostimulants, and serum prolactin concentration.

Results: The sample consisted of 115 patients (87% males) with a mean ($\pm$ SD) age of 11.6 ($\pm$ 2.8) years. The majority had externalizing disorders, and they had taken risperidone for 2.4 ($\pm$ 1.7) years. Body iron was low, with 45% having iron depletion and 14% having iron deficiency. Iron status was inversely associated with weight gain during risperidone treatment and with interleukin-6. Body iron was neither associated with psychiatric symptom severity nor with the daily dose of risperidone and psychostimulants. It was, however, inversely associated with prolactin concentration, which was nearly 50% higher in the iron-deficient group.

Conclusions: Iron depletion and deficiency are prevalent in children and adolescents chronically treated with risperidone. Iron deficiency accentuates the antipsychotic-induced elevation in prolactin. Future studies should confirm this finding and investigate the potential benefit of iron supplementation in antipsychotic-treated patients.

Introduction

IRON IS AN ESSENTIAL MICRONUTRIENT involved in vital functions such as oxygen transport, cellular respiration, and DNA synthesis. In the brain, iron is a cofactor for many enzymes, and is incorporated in various structural and transport proteins (Beard and Connor 2003). Of particular interest from a psychiatric perspective is that iron is a cofactor for tyrosine hydroxylase, the rate-limiting enzyme for catecholamine synthesis (Sachdev 1993).

Findings in animal models of iron deficiency (ID) and from clinical investigations have recently raised interest in the role ID might play in psychopathology. The induction of ID in rats results in behavioral changes including inattention, rescued by psychostimulants (Mohamed et al. 2011). Detailed studies have implicated ID in dopaminergic dysfunction with decreased density of the dopamine transporter and the dopamine D1 and D2 receptors in the basal ganglia (Beard et al. 1994; Nelson et al. 1997; Erikson et al. 2000, 2001; Burhans et al. 2005). Similarly, in children, a history of

ID has been associated with reduced intellectual and motor function and impaired attention and memory (Lozoff et al. 2000). In addition, these children exhibit more anxiety, depression, and social problems, and show an impaired prolactin response to stress, long after iron repletion (Lozoff et al. 2000; Felt et al. 2006).

ID indicated by low serum ferritin concentration has been linked to the severity of attention-deficit/hyperactivity disorder (ADHD) and resistance to psychostimulant treatment (Konofal et al. 2004, 2008; Oner et al. 2008; Calarge et al. 2010). Moreover, low mean corpuscular volume (a marker of ID) at $\sim$ 3 years of age has been associated with reduced response to psychostimulants nearly 3 years later (Turner et al. 2012). This is consistent with findings of persistent dopaminergic signaling impairment when ID occurs in infancy, despite iron repletion (Lozoff and Georgieff 2006).

Therefore, taking advantage of a sizeable group of children and adolescents chronically treated with risperidone, we examined the association between iron status and prolactin concentration. By blocking the dopamine D2 receptors in the anterior pituitary,

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risperidone releases the tonic dopaminergic inhibition on prolactin secretion, leading to hyperprolactinemia (Calarge et al. 2009b). If ID reduces the dopamine D2 receptors' density, we reasoned that risperidone-treated participants with low iron status would have higher prolactin concentrations because, for the same risperidone serum concentration, a larger proportion of their D2 receptors would be blocked. In exploratory analyses, we also investigated the association among iron status, psychiatric symptom severity, and clinical response to psychostimulants and risperidone.

Materials and Methods

Participants

The aims and methods of the parent study have been described (Calarge et al. 2009a, 2010). Briefly, between November 2005 and August 2009, 7–17-year-old patients treated with risperidone for at least 6 months were recruited. Patients receiving concurrent treatment with antipsychotics other than risperidone were excluded. Also excluded were patients with neurological or medical conditions and female patients who were pregnant or using hormonal contraception.

Procedures

The study was approved by the University of Iowa Institutional Review Board. Written assent was obtained from children <14 years old and informed consent from obtained from adolescents and from parents of all patients. A monetary compensation was provided.

Upon enrollment in the parent study, pubertal stage was determined by a physician-conducted examination and, independently, by the participants using pictures, with parental help when necessary (Calarge et al. 2009a). Height was measured to the nearest 0.1 cm and weight was recorded to the nearest 0.1 kg.

A best-estimate diagnosis, following the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR) (American Psychiatric Association 2000), was generated based on a review of the psychiatric record, often supplemented by a brief clinical interview, and a standardized interview of the parent using the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule for Children (Shaffer et al. 2000). For 50 patients, the Child Behavior Checklist (CBCL) was completed (Achenbach and Rescorla 2001).

Iron intake during the week prior to enrollment was estimated using the 2004 Block Kids Food Frequency Questionnaire (Block et al. 2000). This questionnaire includes 77 food items, based on the dietary recall data of the National Health and Nutrition Examination Surveys (NHANES 1999–2002) (Block et al. 2000). It also queries about multivitamin use, assuming that each tablet contains 18 mg of iron.

As described elsewhere (Calarge et al. 2009a, 2010), a morning blood sample was obtained to measure serum risperidone and 9-hydroxyrisperidone concentrations (referred to, henceforth, as risperidone concentration), prolactin, thyroid stimulating hormone (TSH), high-sensitivity C-reactive protein (hsCRP), and interleukin-6 (IL-6). When available ($n = 115$), leftover serum was stored at -80°C until processed for the present study to measure ferritin (sF) and transferrin receptor concentration (sTfR). Although the time interval between when the sample was collected and when the assay was conducted was not correlated with sF (Spearman's $\rho = -0.04$, $n = 116$, $p > 0.6$), it was inversely correlated with sTfR (Spearman's $\rho = -0.32$, $n = 115$, $p = 0.0006$).

Data analysis

Body mass index (BMI) was calculated as weight/height² (kg/m^2). Weight and BMI measurements were converted into age- and sex-specific z scores (Ogden et al. 2002).

Body iron (mg/kg) was estimated using the formula: $-\log(\text{sTfR}/\text{sF}) - 2.8229/0.1207$, with negative values representing tissue ID (Cook et al. 2003). The participants were divided into three iron status groups, defined following the World Health Organization's guidelines: 1) An iron-deficient group having a $\text{sF} < 12 \text{ ng}/\text{mL}$ and $\text{sTfR} \geq 9.13 \mu\text{g}/\text{mL}$ (representing 10% above the assay's upper cutoff of $8.3 \mu\text{g}/\text{mL}$) or having an $\text{sF} \geq 12 \text{ ng}/\text{mL}$ and $\text{sTfR} \geq 9.13 \mu\text{g}/\text{mL}$ (suggesting ID with inflammation), 2) an iron-depleted group with $\text{sF} < 12 \text{ ng}/\text{mL}$ and $\text{sTfR} < 9.13 \mu\text{g}/\text{mL}$, and 3) an iron-replete group with $\text{sF} \geq 12 \text{ ng}/\text{mL}$ and $\text{sTfR} < 9.13 \mu\text{g}/\text{mL}$ (World Health Organization 2011). Following the cutoffs recommended by the manufacturer of the prolactin assay, hyperprolactinemia was defined as a concentration $> 15.2 \text{ ng}/\text{mL}$ in males and $> 23.3 \text{ ng}/\text{mL}$ in females.

To assess associations with iron status, continuous and categorical variables were compared across the three iron status groups using analysis of variance and Fisher's test, respectively. We also used multivariable linear regression analysis to explore the association between body iron and CBCL-based psychiatric symptom severity, the weight-adjusted daily dose of psychostimulants or risperidone, and prolactin concentration, always with adjustment for potential confounders.

All the statistical tests performed were two-tailed, using SAS version 9.2 for Windows (SAS Institute Inc., Cary, NC), with statistical significance set at $\alpha = 0.05$.

Results

Subject characteristics

There was no significant difference in age, sex, duration of risperidone treatment, change in BMI z score between the initiation of risperidone and study enrollment, iron intake, or serum prolactin concentration between participants with available serum samples to determine sF and sTfR data ($n = 115$) and those without ($n = 49$).

The participants were mostly pre- or peri-pubertal, predominantly with externalizing disorders, and had received risperidone treatment for a mean of 2.4 years, primarily targeting irritability and aggression (86%) (Tables 1 and 2). The iron status groups differed significantly only in that depressive disorders were more prevalent in the iron-deficient group and that this group used α_2 -agonists (i.e., guanfacine and clonidine) less frequently.

Compared with the iron-replete group, the iron-depleted group consumed more calories in general ($p < 0.09$), and carbohydrates specifically ($p < 0.04$) (Table 3). Of note, the iron-replete group used multivitamins nearly twice as often as did the other two groups (Table 2).

Iron status

Iron status of the entire sample was quite poor (Table 4). We found only a suggestion of an inverse association between sF and sTfR (Pearson's $\rho = -0.16$, $p < 0.1$). Dietary iron intake was significantly associated with sF (Pearson's $\rho = 0.28$, $p = 0.003$) but not with sTfR or body iron. Overall, the mean body iron content of $-0.47 \text{ mg}/\text{kg}$ indicated tissue ID (Cook et al. 2003). IL-6 was highest in the ID group followed by the iron-depleted group.

We explored whether weight gain following the initiation of risperidone could explain the poor iron status of the participants. After

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE SAMPLE OVERALL AND SPLIT BASED ON IRON STATUS^a

	Total sample n = 115	Iron-deficient n = 16	Iron-deplete n = 52	Iron-replete n = 47	Statistic	p value
Male sex, n (%)	100 (87)	14 (88)	46 (88)	40 (85)	Fisher's exact	>0.9
Age, years, mean (SD)	11.6 (2.8)	11.3 (0.7)	12.2 (0.4)	11.0 (0.4)	$F = 2.34$	>0.1
Tanner stage I/ II/III/IV/V, %	42/15/19/22/9	40/13/13/20/13	33/12/22/24/10	53/15/13/15/4	Fisher's exact	>0.5
Race/Ethnicity, n (%)						
Non-Hispanic white	87 (76)	12 (75)	38 (73)	37 (79)	Fisher's exact	
African American	18 (16)	4 (25)	9 (17)	5 (11)		
Hispanic	8 (7)	0	5 (10)	3 (6)		
Other	2 (2)	0	0	2 (4)		>0.4
Age- and sex-adjusted measures, mean (SD)						
Enrollment BMI z score	0.57 (1.1)	0.51 (0.28)	0.71 (0.15)	0.42 (0.16)	$F = 0.90$	>0.4
Change in BMI z score	0.46 (0.81)	0.45 (0.22)	0.62 (0.13)	0.29 (0.14)	$F = 1.44$	>0.2
Enrollment weight z score	0.51 (1.1)	0.47 (0.27)	0.66 (0.15)	0.36 (0.16)	$F = 0.89$	>0.4
Change in weight z score	0.44 (0.65)	0.53 (0.17)	0.51 (0.10)	0.33 (0.11)	$F = 0.73$	>0.4

^aIron status was defined based on a combination of serum ferritin and transferrin receptor concentration (see Methods) (World Health Organization 2011).

For continuous variables, means (SD) are reported for the total sample and means (SE) are reported for the three "iron status" groups. BMI, body mass index.

controlling for age ($\beta = -0.33$, $p < 0.05$), sex ($\beta = -0.40$, $p > 0.7$), and the interval between the onset of risperidone treatment and study enrollment ($\beta = -0.05$, $p > 0.8$), the change in BMI z score during this interval was inversely associated with estimated body iron ($\beta = -1.30$, $p < 0.02$). Comparable results were found for the association between sF and change in BMI z score ($\beta = -3.44$, $p < 0.02$).

Next, we investigated whether subclinical inflammation could account for the low iron status. We found IL-6 to be inversely related to body iron (Pearson's $\rho = -0.28$, $p < 0.02$) and sF (Pearson's $\rho = -0.20$, $p < 0.1$). There were no significant associations of hsCRP with iron status.

Iron status and prolactin

After controlling for age ($\beta = 0.82$, $p < 0.07$), male sex ($\beta = -7.0$, $p < 0.04$), BMI ($\beta = -0.61$, $p < 0.04$), the weight-adjusted daily dose of psychostimulants ($\beta = 0.86$, $p > 0.4$), and serum risperidone concentration ($\beta = 0.78$, $p < 0.0001$), body iron was inversely associated with serum prolactin concentration ($\beta = -0.65$, $p < 0.02$) (Fig. 1). Comparable results were found when the stage of sexual development was substituted for age or when the time interval between sample collection and TfR assay processing was added to the regression model.

Similarly, after controlling for age ($\beta = 0.87$, $p < 0.06$), male sex ($\beta = -6.43$, $p < 0.06$), BMI ($\beta = -0.50$, $p < 0.08$), the weight-adjusted daily dose of psychostimulants ($\beta = 0.69$, $p > 0.5$), and risperidone concentration ($\beta = 0.78$, $p < 0.0001$), the iron status group was significantly associated with prolactin concentration ($p < 0.005$). In fact, the iron-deficient group had nearly 50% higher prolactin concentration than did the iron-depleted and iron-replete groups, which did not differ from each other (32.3 [se = 3.1] vs. 22.5 [se = 2.1], $p < 0.005$, and vs. 21.2 [se = 2.1], $p < 0.002$, respectively). Again, the results did not substantially change when the stage of sexual development was substituted for age or when the time interval between sample collection and TfR assay processing was added to the regression model.

Iron status and psychopathology

We examined whether body iron was associated with the T score on any of the CBCL factors, and found no significant association

(Spearman's ρ ranged between -0.21 and 0.13). Controlling for the weight-adjusted daily dose of psychostimulants and risperidone did not alter the results.

Iron status and pharmacotherapy

Similarly, we did not find any significant association between body iron and the weight-adjusted daily dose of psychostimulants after controlling for age, sex, and the weight-adjusted daily dose of risperidone. Including the CBCL-based T score on the attention, externalizing, or total problems scales did not alter the results.

We also could not find any significant association between body iron and the weight-adjusted daily dose of risperidone after controlling for age, sex, and the weight-adjusted daily dose of psychostimulants. Including the CBCL-based T score on the rule-breaking, aggression, externalizing, or total problems scales led to comparable findings.

Discussion

To our knowledge, this is the first study to examine, albeit cross-sectionally, iron status after extended antipsychotic treatment. We found ID to be surprisingly prevalent. As predicted, ID was associated with higher prolactin concentration. On the other hand, there was no association either with the severity of psychiatric symptoms or with the dose of the two classes of drugs that directly modulate central dopaminergic signaling.

The majority of the sample had an sF below the recommended cutoff to identify iron stores depletion (World Health Organization 2011). In combination with sTfR, this translated into 14% of the participants having ID with another 45% having iron depletion. These rates far exceed the estimated prevalence of ID, in the United States, of 4% in 6–11-year-olds and of 5% in older boys (Looker et al. 2002). Rather, they are somewhat comparable to the rates observed in infants and menstruating females, known to be at an increased risk for ID (Looker et al. 2002).

Transferrin is a metalloprotein that carries iron in the blood, delivering it to various tissues via TfR. When iron stores are depleted, TfR production increases to promote transferrin binding. As a result, serum TfR concentration also increases. The inverse

TABLE 2. PSYCHIATRIC CHARACTERISTICS OF THE SAMPLE OVERALL AND SPLIT BASED ON IRON STATUS^a

	Total sample n = 115	Iron-deficient n = 16	Iron-deplete n = 52	Iron-replete n = 47	Statistic	p value
Psychopathology						
Attention-deficit/hyperactivity disorder (ADHD), n (%)	106 (92)	14 (88)	47 (90)	45 (96)	Fisher's exact	>0.3
Disruptive behavior disorder, n (%)	106 (92)	13 (81)	48 (92)	45 (96)	Fisher's exact	>0.1
Anxiety disorder, n (%)	31 (27)	5 (31)	14 (27)	12 (26)	Fisher's exact	>0.9
Tic disorder, n (%)	23 (20)	2 (13)	11 (21)	10 (21)	Fisher's exact	>0.8
Pervasive developmental disorder, n (%)	14 (12)	1 (6)	7 (13)	6 (13)	Fisher's exact	>0.8
Depressive disorder, n (%)	10 (9)	4 (25)	4 (8)	2 (4)	Fisher's exact	<0.05
Psychosis, n (%)	1 (1)	1 (6)	0	0	Fisher's exact	>0.1
Child Behavior Checklist (n=50), T scores						
Anxious/Depressed	64.2 (11.1)	59.3 (3.9)	67.2 (2.5)	63.6 (2.3)	F = 1.54	>0.2
Withdrawn/Depressed	62.7 (8.4)	60.9 (2.9)	66.1 (1.9)*	60.4 (1.7)*	F = 2.77	<0.08
Somatic complaints	58.9 (7.8)	56.4 (2.8)	59.2 (1.8)	59.5 (1.7)	F = 0.49	>0.6
Social problems	66.6 (9.0)	61.1 (3.1)*	69.9 (2.0)*	65.7 (1.8)	F = 3.17	<0.06
Thought problems	68.1 (8.8)	69.6 (3.1)	69.2 (2.0)	66.6 (1.9)	F = 0.59	>0.5
Attention problems	69.2 (10.2)	74.9 (3.6)	67.7 (2.3)	68.3 (2.1)	F = 1.54	>0.2
Rule-breaking behavior	64.4 (7.9)	63.8 (2.9)	63.8 (1.9)	65.0 (1.7)	F = 0.13	>0.8
Aggressive behavior	71.0 (12.1)	67.6 (4.3)	73.4 (2.8)	70.3 (2.5)	F = 0.71	>0.4
Internalizing problems	60. (9.0)	60.3 (3.1)	66.6 (2.0)	62.1 (1.8)	F = 1.97	>0.1
Externalizing problems	67.7 (9.7)	66.4 (3.5)	68.9 (2.3)	67.2 (2.0)	F = 0.25	>0.7
Total problems	69.0 (7.8)	67.9 (2.8)	70.5 (1.8)	68.1 (1.6)	F = 0.57	>0.5
Psychopharmacology						
Risperidone dose, mg/kg/day, mean (SD)	0.03 (0.02)	0.03 (0.01)	0.03 (0.00)	0.04 (0.00)	F = 1.15	>0.3
Serum concentration, ng/mL, mean (SD)	10.6 (11.7)	10.0 (2.9)	9.4 (1.6)	12.2 (1.7)	F = 0.76	>0.4
Treatment duration, years, mean (SD)	2.4 (1.7)	2.2 (0.4)	2.7 (0.2)	2.2 (0.2)	F = 0.94	>0.3
Psychostimulants, n (%)	85 (74)	12 (75)	39 (75)	34 (72)	Fisher's exact	>0.9
Psychostimulants dose, mg/kg/day, mean (SD)	1.4 (0.8)	1.3 (0.2)	1.3 (0.1)	1.6 (0.1)	F = 1.26	>0.2
Treatment duration, years, mean (SD)	5.3 (2.6)	4.8 (0.8)	5.5 (0.4)	5.2 (0.5)	F = 0.31	>0.7
Serotonin reuptake inhibitor (SSRIs), n (%)	52 (45)	7 (44)	23 (44)	22 (47)	Fisher's exact	>0.9
α_2 -agonists, n (%) ^b	37 (32)	1 (6)	17 (33)	19 (40)	Fisher's Exact	<0.04
Multivitamin use, n (%)	36 (31)	4 (25)	11 (21)	21 (45)	Fisher's Exact	<0.04

Statistically significant results ($p < 0.05$) are bolded and those suggestive of an association ($p < 0.1$) are bolded and italicized. For continuous variables, means (SD) are reported for the total sample and means (SE) are reported for the three "iron status" groups.

^aIron status was defined based on a combination of serum ferritin and transferrin receptor concentration (see Methods) (World Health Organization 2011).

^bThese include guanfacine and clonidine frequently used to treat ADHD, insomnia, and disruptive behavior.

* $p < 0.10$.

association we found between sTfR and the interval between sample collection and assay processing suggests that TfR degrades over time, even if stored at -80°C . Because we defined iron status based on a combination of reduced sF and increased sTfR (World Health Organization 2011), the degradation of TfR with storage time underestimates the true rate of iron depletion/deficiency in our sample. Therefore, particular attention should be paid to identifying and addressing the poor iron status in this already vulnerable population, particularly as ID has been implicated in impaired cognitive and psychiatric functioning (Grantham-McGregor and Ani 2001; Konofal et al. 2004; Calarge et al. 2010).

The high degree of iron depletion/deficiency could have resulted from the rapid increase in weight and BMI following the initiation of risperidone. Weight gain associated with antipsychotic medications can be substantial (Calarge et al. 2009a, Correll et al. 2009).

We found that the more the participants grew, in excess to what would be developmentally expected, the lower their body iron was. This is reminiscent of the accentuated risk for ID observed in infancy, a developmental period characterized by accelerated growth (Georgieff et al. 2002; Fuglestad et al. 2008; Yang et al. 2009). A 0.44 increase in weight z score in an 11.6-year-old boy, representative of the participants (Table 1), translates into nearly four additional kilograms. Assuming a blood volume of 85 mL/kg of body weight, a hemoglobin concentration of 12 g/dL, and the need for 3.46 mg of iron to synthesize a gram of hemoglobin, this increase in weight would require the absorption of an estimated 141 mg of iron. This is in addition to what would be needed for age-appropriate growth; an estimated 1 mg of iron (2 mg in menstruating women) is absorbed daily to replace losses in adults (Fuqua et al. 2012). Importantly, if iron intake or absorption are suboptimal, the available

TABLE 3. DIETARY INTAKE OF THE SAMPLE OVERALL AND SPLIT BASED ON IRON STATUS^a

	Total sample n = 113 ^b	Iron-deficient n = 15	Iron-deplete n = 51	Iron-replete n = 47	Statistic	p value
Total calories, kcal/day	1838 (711)	1704 (181)	2011 (98)*	1694 (103)*	$F = 2.83$	<0.07
Protein, g/day	63.7 (24.7)	63.1 (6.4)	67.3 (3.5)	60.0 (3.6)	$F = 1.07$	>0.3
Fat, g/day	65.4 (27.9)	63.9 (7.2)	70.1 (3.9)	60.8 (4.0)	$F = 1.41$	>0.2
Carbohydrates, g/day	255.7 (104.1)	224.5 (26.2)	285.5 (14.2)**	233.3 (14.8)**	$F = 4.06$	<0.02
Iron, mg/day ^c	16.1 (7.2)	13.4 (1.9)	15.8 (1.0)	17.3 (1.1)	$F = 1.76$	>0.1
Zinc, mg/day ^c	12.8 (5.7)	10.9 (1.5)	12.6 (0.8)	13.5 (0.8)	$F = 1.17$	>0.3
Vitamin C, mg/day ^c	118.4 (77.3)	94.7 (19.7)	135.9 (10.7)	107.1 (11.1)	$F = 2.59$	<0.08
Total fiber, g/day	12.9 (5.8)	12.0 (1.5)	14.0 (0.8)	12.1 (0.8)	$F = 1.46$	>0.2
Beans fiber, g/day	1.2 (1.4)	1.0 (0.4)	1.3 (0.2)	1.1 (0.2)	$F = 0.41$	>0.6
Vegetables/Fruits fiber, g/day	4.3 (3.3)	3.6 (0.8)	5.2 (0.5)**	3.5 (0.5)**	$F = 3.48$	<0.04
Grains fiber, g/day	4.4 (2.0)	4.1 (0.5)	4.6 (0.3)	4.3 (0.3)	$F = 0.37$	>0.6

^aIron status was defined based on a combination of serum ferritin and transferrin receptor concentration (see Methods) (World Health Organization 2011).

^bTwo participants with invalid dietary data were excluded.

^cThis combines intake from food and supplements (i.e., multivitamins).

* $p < 0.10$.

** $p < 0.05$.

For continuous variables, means (SD) are reported for the total sample and means (SE) are reported for the three “iron status” groups. Statistically significant results ($p < 0.05$) are bolded and those suggestive of an association ($p < 0.1$) are bolded and italicized.

TABLE 4. LABORATORY MEASURES IN THE SAMPLE OVERALL AND SPLIT BASED ON IRON STATUS^a

	Total sample n = 115	Iron-deficient n = 16	Iron-deplete n = 52	Iron-replete n = 47	Statistic	p value
Ferritin concentration, ng/mL, mean (SD) ^b	12.6 (10.3)	9.4 (1.7)	5.4 (1.0)	21.7 (1.0)	$F = 70.55$	<0.0001
Ferritin < 15 ng/mL, n (%)	72 (63)	14 (88)	52 (100)	6 (13)	Fisher's exact	<0.0001
Ferritin < 12 ng/mL, n (%)	63 (55)	11 (69)	52 (100)	0	Fisher's exact	<0.0001
Ferritin < 7 ng/mL, n (%)	34 (30)	5 (31)	29 (56)	0	Fisher's exact	<0.0001
Collection-assay interval, years, mean (SD)	3.6 (1.3)	3.4 (0.3)	3.7 (0.2)	3.5 (0.2)	$F = 0.39$	>0.6
Transferrin receptor concentration (sTfR) $\mu\text{g/mL}$, mean (SD)	7.2 (6.7)	17.5 (1.3)	5.6 (0.7)	5.4 (0.8)	$F = 35.90$	<0.0001
sTfR > 8.3 $\mu\text{g/mL}$, n (%)	19 (17)	16 (100)	2 (4)	1 (2)	Fisher's exact	<0.0001
Collection-assay interval, years, mean (SD)	3.9 (1.3)	3.8 (0.3)	4.0 (0.2)	3.8 (0.2)	$F = 0.40$	>0.6
Body iron, mg/kg, mean (SD)	-0.47 (4.47)	-4.26 (0.77)	-2.81 (0.43)	3.41 (0.45)	$F = 64.87$	<0.0001
Body iron < -4 mg/kg, n (%) ^c	22 (20)	4 (25)	18 (37)	0	Fisher's exact	<0.0001
Prolactin concentration, ng/mL, mean (SD)	21.0 (14.8)	29.4 (3.6)	18.9 (2.0)	20.4 (2.1)	$F = 3.29$	<0.05
Hyperprolactinemia, n (%) ^d	69 (60)	11 (69)	32 (62)	26 (55)	Fisher's exact	>0.6
High-sensitivity C-reactive protein (hsCRP) concentration, mg/L, mean (SD) ^e	0.7 (1.5)	0.4 (0.5)	1.0 (0.3)	0.5 (0.3)	$F = 1.28$	>0.2
hsCRP > 5 mg/L, n (%) ^e	3 (4)	0	3 (9)	0	Fisher's exact	>0.2
Interleukin (IL)-6 concentration (log), pg/mL, mean (SD) ^e	-0.01 (0.73)	0.41 (0.21)	0.07 (0.12)	-0.30 (0.14)	$F = 4.34$	<0.02
Thyroid stimulating hormone (TSH) concentration, $\mu\text{IU/mL}$, mean (SD)	2.6 (1.2)	2.3 (0.3)	2.6 (0.2)	2.8 (0.2)	$F = 0.78$	>0.4
TSH < 4.2 $\mu\text{IU/mL}$, n (%) ^f	99 (86)	16 (100)	45 (87)	38 (81)	Fisher's exact	>0.1

^aIron status was defined based on a combination of serum ferritin and transferrin receptor concentration (see Methods) [26].

^bA cutoff of 15 ng/mL is recommended by the World Health Organization to define iron stores depletion in the absence of infection [26]. A cutoff of 7 ng/mL is the lower limit of normal based on the sF assay manufacturer.

^cAn body iron content of < -4 mg/kg has been used as a marker of iron deficiency anemia (Cook et al. 2003). Three participants with hsCRP > 5 mg/L were excluded from this particular analysis.

^dHyperprolactinemia was defined as a prolactin concentration > 15.2 ng/mL in boys and > 23.3 ng/mL in girls.

^eHigh sensitivity C-reactive protein and interleukin-6 were available for only 69 participants.

^fIn no case was TSH > 6.9 $\mu\text{IU/mL}$.

For continuous variables, means (SD) are reported for the total sample and means (SE) are reported for the three “iron status” groups. Statistically significant results ($p < 0.05$) are bolded and those suggestive of an association ($p < 0.1$) are bolded and italicized.

FIG. 1. Correlation of serum prolactin concentration (ng/mL) and body iron (mg/kg), after controlling for age, sex, body mass index, the weight-adjusted dose of psychostimulants, and serum risperidone concentration. Body iron was estimated using the formula: $-\log(sTfR/sF)-2.8229/0.1207$, with negative values representing iron depletion in relation to the needed stores to maintain normal hemoglobin concentration (Cook et al. 2003).

body iron will be prioritized to hemoglobin synthesis at the expense of other tissues, including the brain (Georgieff et al. 1990; Guiang et al. 1997).

Another potential mechanism contributing to ID is subclinical inflammation associated with obesity (del Giudice et al. 2009; Cepeda-Lopez et al. 2010). IL-6, a pro-inflammatory cytokine, is a prominent inducer of hepcidin release (Nemeth and Ganz 2009). This, in turn, inhibits iron transport across membranes by down-regulating the transport protein ferroportin. As a result, less iron is absorbed, reducing iron stores, including in the brain (Nemeth and Ganz 2009; Fuqua et al. 2012).

It has been suggested that anorexia induced by psychostimulants can reduce iron intake, thus accounting for the low sF observed in children with ADHD (D'Amato 2005). However, we could not support this contention in our previous work (Calarge et al. 2010) and have again found, in this sample, that the daily consumption of iron largely meets the recommended dietary allowances for this predominantly male group of participants (Trumbo et al. 2002). It is of significance that the use of multivitamins was almost double in the iron-replete group than in the other two groups, although the estimated overall daily iron intake did not differ among them. Importantly, the bioavailability of iron varies substantially depending upon various factors, including body iron status and dietary intake (Benito et al. 1998; Hurrell and Egli 2010). We did not find a difference in the intake of vitamin C, zinc, total fiber, or, more specifically, the intake of fiber from grains, across the three iron status groups, although the iron-depleted group consumed more fiber from vegetables and fruits than did the iron replete group (Table 4). More detailed dietary and bioavailability studies are needed to thoroughly address this issue. In addition, whether the iron depletion/deficiency we report corrects over time, as excessive growth plateaus, remains to be seen.

One of the most replicated findings in iron-deficient rodents is the reduction in the density of dopamine D2 receptors (Erikson et al. 2001). In pituitary lactotrophs, this receptor is tonically activated by dopamine, suppressing prolactin release. When blocked by agents such as risperidone, hyperprolactinemia ensues (Calarge et al. 2009b). This can be concerning in light of evidence implicating risperidone-induced hyperprolactinemia in the disruption of

bone mineralization in youth (Calarge et al. 2010). As predicted, prolactin concentration was higher with lower body iron stores. This is consistent with findings in ID rats treated with haloperidol (Barkey et al. 1986). It suggests that improving iron status might alleviate hyperprolactinemia following chronic risperidone treatment. Notably, Felt et al. have found, in their sample of children with a history of ID in infancy, impaired prolactin response to stress long after iron status had been corrected (Felt et al. 2006). As we did not assess iron status at the onset of risperidone treatment, it is unknown for how long the participants had been iron deficient/depleted and whether correcting iron status would reduce prolactin, a hypothesis worth testing. Moreover, there might be a "threshold" of iron depletion required before this association becomes of clinical significance. In fact, whereas hyperprolactinemia was prevalent in all three iron status groups, prolactin was significantly higher only in the iron-deficient group compared with the other two groups, which did not differ from each other.

Low sF has been associated with ADHD symptom severity as well as resistance to psychostimulant treatment (Konofal et al. 2004; Cortese et al. 2008; Calarge et al. 2010; Turner et al. 2012). This is thought to be related to ID impairing dopaminergic signaling (Beard and Connor 2003). However, although sF in our sample was the lowest compared with the other studies in psychiatric samples, we failed to find a significant association between body iron and either psychiatric symptoms or the dose of psychostimulants and risperidone, drugs that directly affect the dopaminergic system. Several reasons could explain our findings, including the possibility that pharmacotherapy masked an association of body iron with symptom severity or that the CBCL is not specific enough to fully capture externalizing symptoms, although this is a well-validated and widely used broad-based measure. Furthermore, unlike other studies in which the participants were unmedicated, our participants received multiple psychotropics concurrently. This could have obscured a possible association between body iron and medication dose. Finally, it is possible that dose is not an appropriate surrogate for sensitivity to these medications and, consequently, the integrity of the dopaminergic system.

The prevalence of depression was the highest in the iron-deficient group with the iron-depleted group exhibiting the highest T score on

the withdrawn/depressed and social problems scales of the CBCL (Table 2). These findings could have emerged by chance because of the number of comparisons conducted (i.e., type 1 error). Nonetheless, they are somewhat consistent with work by others showing increased internalizing symptoms in children with a history of ID anemia (Lozoff et al. 2000). In contrast, the use of serotonin reuptake inhibitors (SSRIs), which have been associated with elevated prolactin (Emiliano and Fudge 2004), was not different across the three iron status groups. We elected not to include SSRIs in the model, as they failed to affect prolactin concentration in a previous analysis we conducted, using a partially overlapping sample (Calarge et al. 2009b). It is possible that they may affect combined risperidone and 9-hydroxy-risperidone concentration (Calarge and Miller 2011); however, this is already one of the predictors in the model. Adding SSRIs ($p > 0.4$) to the model predicting prolactin concentration did not substantially alter our findings.

Limitations

This study has several limitations. Most significantly, the effect of time on TfR stability underestimates the rate of ID in the sample. Furthermore, as the primary aims of the study were unrelated to iron status, we did not measure hemoglobin. This prohibited estimating the prevalence of ID anemia. Nonetheless, neither of these shortcomings should affect the validity of the findings from the correlational analyses. The serum samples were collected long after the participants had started psychopharmacology; therefore, it is not possible to establish whether iron depletion preceded the onset of treatment or followed as is suggested by the inverse association between excessive weight gain and body iron. Moreover, this also leaves unanswered the possibility that risperidone or pharmacotherapy might directly interfere with iron bioavailability. It is of note that in our previous study in children with ADHD, sF averaged ~ 18 ng/mL although the majority of the participants had been medication naïve (Calarge et al. 2010). Furthermore, in patients with autistic disorder, risperidone was not associated with a significant decline in sF (Arnold et al. 2010). This latter finding, however, might be because of the relatively short duration of that trial (i.e., 8 weeks). In fact, using plasma samples from another risperidone trial in pervasive developmental disorders (PDD) (Aman et al. 2009), we recently confirmed the inverse association between risperidone-induced weight gain and reduction in ferritin concentration (Del Castillo et al. 2012). Interestingly, unlike our previous study in ADHD (Calarge et al. 2010), baseline ferritin in these participants with PDD was normal (33.4 ± 23.4 ng/mL). Therefore, whether ferritin concentration prior to antipsychotic treatment is normal may depend upon the clinical population. However, once the antipsychotic is initiated, rapid weight gain will worsen iron status regardless of diagnosis. Finally, a prospective study with a better representation of females and of youth from diverse ethnic/racial backgrounds is necessary to replicate our findings and establish their generalizability. Moreover, a much larger sample is necessary to explore the interplay among hyperprolactinemia, iron status, and variants of the dopamine D2 receptor gene, which we have shown, in a partially overlapping sample, to moderate the risk for risperidone-induced hyperprolactinemia (Calarge et al. 2009b).

Conclusions

In a cross-sectional study of children chronically treated with risperidone, iron depletion and deficiency were prevalent. Moreover, there was an inverse association between the severity of low

body iron stores and elevation in prolactin, potentially reflecting deficit in central dopaminergic signaling.

Clinical significance

As the use of antipsychotics in children and adolescents continues to grow (Comer et al. 2010), optimizing their safety in light of their potential to cause weight gain and cardiometabolic abnormalities, and to impair bone mineralization is paramount (Calarge et al. 2009a; Correll et al. 2009; Calarge et al. 2010.). Another possible adverse event that has gone unrecognized so far is iron depletion/deficiency. This may emerge in association with the rapid and excessive weight gain observed with these medications. ID with and without anemia has been implicated in impaired cognitive and psychiatric functioning (Grantham-McGregor and Ani 2001; Konofal et al. 2004; Calarge et al. 2010). Therefore, until prospective studies more rigorously explore this question, our findings suggest that it may be cautious to monitor for and prevent iron depletion in youth receiving chronic antipsychotic treatment.

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Disclosures

Drs. Calarge and Ziegler had no conflicts of interest or financial ties to report.

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