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Randomized study of cognitive effects of iron supplementation in non-anemic iron-deficient adolescent girls

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Abstract: **This double-blind, placebo-controlled clinical study evaluated the effects of iron supplementation on cognitive function in adolescent girls with non-anaemic iron deficiency. Methods Seven hundred and sixteen girls enrolled in four Baltimore high schools were evaluated for nonanemic iron deficiency (serum ferritin <12 µg/L with normal hemoglobin). Ninety-eight (13.7%) girls were non-anemic iron deficient, of whom 81 subjects were randomized to receive oral iron sulfate (650 mg twice daily) or placebo for 8 weeks. The effect of iron treatment was assessed using questionnaires, hematological and cognitive tests administered before the start of treatment and repeated after the procedure. Results Of the 81 non-anemic iron-deficient girls, 78 (96%) completed the study (39 in each group). Five girls (three control, two treatment girls) developed anemia during the intervention and were excluded from the analyses. Ethnic distribution, mean age, serum ferritin concentrations, hemoglobin concentrations and cognitive test results of the groups did not differ significantly at baseline. The hematological measurements of the iron status after the intervention improved significantly in the treatment group (serum ferritin 27.3 vs. Regression analysis showed that girls who received iron performed better than girls in the control group on a test of verbal learning and memory (p<0.02).Interpretation In this urban population of nonanemic iron-deficient adolescent girls, iron supplementation improved verbal learning and memory.**

Keywords: **iron supplementation, adolescent girls, nonanemic iron deficiency, verbal learning, memory.**

I. INTRODUCTION

This disorder is not limited to developing countries, and is the main cause of anaemia in the USA. Iron deficiency is a systemic condition, which has many non-haematological consequences: it impairs physical endurance, work capacity, infant growth and development, and depresses immune function. Since the initial studies by Oski and Honig,4 most research on the cognitive effects of iron deficiency has focused on infants and very young children (toddlers). Several studies have shown that iron deficiency causes changes in behaviour and lowers development test scores in infancy.5,6 Animal models have revealed several mechanisms by which iron deficiency may affect cognition; these include changes in brain iron content and distribution, and in neurotransmitter function. 10 During the past 10 years, the increased use of iron-fortified formulas and cereals has improved the iron status of children and reduced the prevalence of iron-deficiency anaemia.11 However, adolescent girls and young women are still at high risk of developing iron deficiency because of increased iron demands during puberty, menstrual losses, and limited dietary iron intake. Prevalence estimates of iron deficiency in adolescent girls range from 9% to 40%, depending on the population studied and the criteria used to define iron deficiency. Ballin and colleagues 15 found that iron-treated adolescent girls reported decreased lassitude and improved mood and ability to concentrate. Many studies of the systemic effects of iron deficiency have focused on individuals with iron-deficiency anaemia. Thus, a better understanding of the possible cognitive effects of iron deficiency in the absence of anaemia is particularly important because of the high rate of this condition in adolescent girls. The main aim of this randomised, double-blind, placebo-controlled trial was to examine the effects of iron supplementation on attention, memory, and learning in non-anaemic iron-deficient adolescent girls.

II. METHODS

During August and September, 1993, girls who enrolled at the four schools (grades 9–12 [ages 13–18]) were asked to take part in a voluntary screening for iron deficiency, which consisted of a complete blood count and measurement of serum ferritin concentration. Hemoglobin concentrations were obtained from a complete blood count, and serum ferritin was measured by chemiluminometric immunoassay (CIBA Corning Diagnostic Corporation, Norwood, Massachusetts, USA). Anemia was defined as a hemoglobin concentration of less than 11·5 g/dL for African American girls or less than 12·0 g/dL for white girls. 17 Non-anemic iron deficiency was defined as a serum ferritin concentration of less than 12·0 μg/L with a normal hemoglobin concentration. 18,19 Only girls with non-anaemic iron deficiency were eligible for enrolment in the trial.

After we obtained written informed consent from the student and a parent or guardian, eligible participants were randomly assigned to a treatment or control group. Standard cognitive tests were administered by trained research assistants at the participants' schools; three measures of attention and one multicomponent test of verbal learning and memory were used. The Brief Test of Attention (BTA)20 is a measure of auditory divided attention, in which participants listen to a tape of letters and numbers (eg, 4-A-8-G-3-2) and are asked to report how many numbers or letters they hear. Participants were randomly allocated a non-prescription ferrous sulphate preparation (Feosol, SmithKline Beecham) or Iron and placebo (SmithKline Beecham) tablets were identical in appearance and dose regimen. Research assistants were unaware of treatment allocation throughout the study; treatment received was not disclosed until all subjects had completed postintervention testing.

Research assistants administered one dose of treatment or placebo every school day; on weekends and holidays girls were contacted at home and reminded to take their tablets. In addition, researchers worked closely with girls and their families to encourage continuing participation, monitor compliance, and ask about side-effects. Every week girls received their supply of tablets and were asked to report any doses that they had not taken. After treatment had stopped, hematological and cognitive tests were repeated and participants completed a brief questionnaire about their group assignment (iron, placebo, don't know), any side-effects (nausea, stomach ache, headache, diarrhea, change in stool color, constipation, other); and behavioral and cognitive changes in energy, attention, memory, mood, and sleep pattern (more/better, the same, less/worse). We estimated that 70 participants (35 in each group) were required to detect a 0·5 SD change in cognitive test scores by a one-tailed Students' t test (α=0·05, β=0·1).

III. RESULTS

Of these 716 girls, 112 (16%) were iron deficient—14 had iron-deficiency anaemia and 98 were not anaemic and therefore eligible to enrol in the trial. After the 8-week intervention, the treatment group had a significantly higher mean serum ferritin concentration Similarly, girls who took iron had a significantly higher mean haemoglobin concentration We used multiple-linear regression analysis to assess the effect of iron treatment on postintervention cognitive test scores, after adjustment for baseline scores. Iron treatment had no significant effect on postintervention BTA, SDM T, or VSAT scores (the three measures of attention). However, on the total recall score of the HVLT (sum of trials 1–3), girls who took iron showed significant improvement over baseline and end of treatment compared with the control group (p<0·02). Baseline performance on the HVLT accounted for 93% of the variability in postintervention scores, whereas treatment condition accounted for the remainder. After adjustment for baseline scores, the correlation between the change in serum ferritin and postintervention score on the HVLT was 0·21 (p=0·04). We compared preintervention and postintervention scores on each trial of the HVLT to assess differences detected between groups in total HVLT scores. We used ANOVA to analyse the HVLT learning curve by group assignment (treatment or control), session (baseline or postintervention), and trial (three free recall trials per test All girls recalled more words at each successive trial ($F_{2,142}$ =273·70, p<0·001) with no significant differences between groups. Although both groups did better after the intervention ($F_{1,71}$ =6·30, p<0·02), girls who took iron recalled more words at each successive trial than girls in the control group. postintervention questionnaire on side-effects, subjective behavior, and cognitive changes . There was no significant difference between groups when girls were asked to guess whether they had taken iron or placebo: 21 (62%) girls in the treatment group and 14 (45%) in the control group correctly guessed their group assignment (p=0·18). Regression analysis did not show any association between cognitive performance and which intervention girls thought they had received. However, significantly more iron-treated girls reported changes in stool color than girls in the control group (22 [65%] vs 3 [10%], p<0·001). We found no significant differences in energy, mood, or attention; a few more girls who took iron reported slightly more improvement in memory than girls in the control group (7 [21%] vs 3 [10%], p=0·20).

IV. DISCUSSION

The findings suggest that, even in the absence of anaemia, iron supplementation improves some aspects of cognitive functioning in iron-deficient adolescent girls. The positive effect of iron supplementation on verbal learning and memory was shown in both the per-protocol and intention-to-treat analyses. Our findings in adolescent girls accord with previous research on infants and toddlers in whom iron deficiency had a negative effect on language development. The effect of iron therapy on learning, shown by the increased HVLT scores of the treatment group, raises questions about the overall effects of iron deficiency on cognition. This finding may have been due to the small number of participants, because our study was designed to detect significant changes on total cognitive test scores rather than subtest or trial scores.

Animal models show that iron deficiency is associated with changes in: neurotransmitter synthesis, uptake, and degradation; mitochondrial function; brain iron deposition; protein synthesis; and oxidation-reduction and electron transport. However, one study27 showed an association between ferritin concentrations and electroencephalographic asymmetry, and another 28 observed changes in urinary catecholamines in iron deficient infants, which returned to normal after iron therapy. Clearly, the association between iron status and cognition is complex, and further research is needed. Our study focused on the effects of iron deficiency in the absence of anemia in a cohort of adolescent girls. More than 6% of the girls developed iron-deficiency anemia during the study.

By contrast, Fordy and Benton 29 measured ferritin concentrations in young men and women and found no association between low iron status and psychological functioning. One possible explanation for these conflicting findings is that the effect of iron deficiency on cognitive function may be subtle. We did not assess whether there were any baseline differences in cognitive functioning between normal and iron-deficient adolescents. For example, mean baseline scores on the BTA were at or near 100% of the possible test score in both groups; this ceiling effect may have limited the ability of the BTA to detect any changes in attention between the groups. We assessed the effects of iron supplementation only on standardized cognitive tests; further research is needed to assess whether such cognitive effects are limited to neuropsychological measures or are also evident in academic performance.

This study suggests that, even in the absence of anemia, iron supplementation improves verbal learning and memory among adolescent girls, which suggests that further investigations of the non-hematological effects of iron deficiency are warranted.

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