Iron therapy and anthropometry: A case-control study among iron deficient preschool children

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doi: https://doi.org/10.1016/j.epag.2017.07.001

Keywords:
Iron deficiency anemia
Growth velocity
Children

INTRODUCTION

Iron deficiency anemia (IDA) is a global public health problem affecting 1.62 billion people, with the highest prevalence in preschool children (47%) especially in third world countries.1-3. Increased demands make infants and children at special risk group. Providing additional dietary iron to infants is not easy, as their needs are usually not covered by fortification programs.4,5

Iron plays an important role in children’s growth and development, such as brain development, cognitive function, motor function, behavior, and immunity. There is enough evidence that showed that decreased appetite, endocrinologic alterations, neurotransmitter metabolism changes, increased metabolic rate, increased catabolism resulting in enhanced morbidity may contribute to the adverse effects of iron deficiency.6

The important effects of iron on growth can be explained by its essential role in multiple metabolic processes, including oxygen transport, DNA synthesis and electron transport.7 In addition, iron deficiency may affect growth through IGF-I dependent mechanism; IGF-I concentration has an important relationship to iron metabolism and protoporphyrin synthesis in children and adolescents.8 In IDA, plasma norepinephrine, cortisol, parathyroid hormone, urinary excretion of epinephrine and norepinephrine are increased.9 Elevation of both of the norepinephrine levels in the blood and urine and the metabolic rate of the IDA subjects lead to slower growth rates and lower body weights of IDA subjects.10,11 Furthermore, the effects of IDA on growth were shown to be resistant even to the administration of growth hormone.12,13 Moreover, thyroid

OBJECTIVE

To investigate the iron status of preschool children with IDA and its association with the degree of growth retardation at presentation, and to detect the effect of iron supplementation on growth velocity (GV) over a period of one year.

MATERIALS AND METHODS: A case-control study conducted in Diabetes Endocrine Metabolism Pediatric Unit in collaboration with the Pediatric Hematology clinic at Children’s Hospital, Cairo University included baseline and follow up anthropometric and hematological parameters of 40 IDA patients with mean age 2 ± 0.8 years compared to 40 healthy clinically non-anemic, age and sex-matched controls with mean age 2.7 ± 1.1 years. A daily total dose of 6 mg/kg/day of ferrous sulfate in 2–3 divided doses were given between meals to patients with IDA.

RESULTS: At presentation, patients with IDA had low hemoglobin, hematocrits, serum iron, serum ferritin, height standard deviation score (SDS), weight SDS, and body mass index (BMI) SDS which improved significantly after treatment. The GV of IDA patients correlated significantly with serum ferritin concentration and also their BMI SDS correlated significantly with the serum ferritin concentration.

CONCLUSION: IDA during the first 6 years of life, when growth is fast, adversely affects both linear growth and weight gain which is reversible with iron therapy, thus adequate iron status is crucial for normal growth (height, weight and GV). The findings of the present study supported the beneficial effects of oral iron supplementation on physical growth parameters of IDA preschool children.

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gland metabolism is also affected with abnormal thermoregulation and a hyper-adrenergic state seen in hypothyroid individuals suffering from IDA. Appetite is decreased in IDA independently of plasma leptin levels, but it may improve with iron supplementation.

Studies regarding the effect of iron on linear growth have shown heterogeneous results. Some studies indicate that iron supplementation of iron deficient infants leads to slower-length gain and others concluded opposing results. Therefore this study aimed at investigating the iron status in preschool children with IDA and its association with the degree of growth retardation at presentation, and detecting the effect of iron supplementation on growth velocity in preschool children.

**Subjects and methods**

**Subjects**

The study was a case-control study conducted from April 2010 to March 2012. The baseline screening included all children attending the Pediatric Hematology Clinic, New Children’s Hospital Cairo university fulfilling the following inclusion criteria: 1) age between 6 months and 5 years; 2) IDA was diagnosed based on conventional clinical manifestations and the following laboratory results (low hemoglobin (Hb) (<10 gm/dl), low hematocrit (Hct) (<33%), microcytic hypochromic picture in the blood film, low serum ferritin (<10 mg/dl) and low serum iron (<30 µg/dl); 3) completing the follow up visits till the end of the study. Patients whose lengths (heights) SDS were more than (+2SD) or less than (−2 SDS) according to the percentile curves for the Egyptian children, or with past history of prematurity or were born small for date or with any identified causes of retarded growth or with a chronic systemic illnesses (renal, cardiac, hepatic, endocrine, nutritional) or taking nutritional supplements containing iron prior to the start of the study were also excluded. This study was carried on two groups of children; the patient group was started by 65 infant and children with IDA, 25 patients of them were excluded as 13 patients showed resistance to oral iron therapy, and need further investigations, while another 12 patients couldn’t complete their follow up visits till the end of the study for un-known causes. Therefore, only 40 patients (34 males and 6 females), completed this study. The control group included another 40 healthy clinically non-anemic, age and sex-matched recruited from healthy infants and children attending the general pediatric clinics at the New Children’s Hospital. The protocol was approved by the local research ethics committee of the pediatric department at Cairo University and all the subjects’ guardians gave informed consent.

**Methods**

The records of all IDA patients and the baseline and data of follow-up visits were reviewed with emphasis on the age at presentation, symptoms of IDA, complete clinical examination; (signs of IDA and to exclude any signs of systemic diseases), and anthropometric assessment. Anthropometric measurements were done according to the recommendations of International Biological Program at the Diabetes Endocrine metabolism Pediatric Unit (DEMPU) outpatient clinic. Anthropometric measurements (including the stature (length for subjects <36 months; height for those ≥36 months) and weight) were taken by the same individual who was duly trained for the task according the adopted protocol at DEMPU at baseline and at follow-up visits. BMI was calculated as weight in kg/height in m2 and BMI (after age 36 months) for all subjects. To calculate BMI for subjects aged <36 months, recumbent lengths were converted to heights by subtracting 0.8 cm. The height (or recumbent length) was measured by using a Harpenden stadiometer (or infantometer) and recorded to the nearest 0.1 cm, and the weight was measured by using self-calibrating electronic SECA scale that records to the nearest 0.1 kg. Parental heights were recorded to calculate target height SDS. Measurements were taken and recorded every 3 months for all subjects and the Growth vision computer software provided by Novo Nordisk was employed to assess weight standard deviation score (SDS) and length/height SDS to assess linear growth. Growth velocities (GV) and GV SDS during the period of study were calculated for both groups using the same computer software.

**Laboratory investigations**

Complete blood count (CBC) was performed for all patients and controls with determination of different indices as Mean Corpuscular Volume (MCV) in fl, Mean Corpuscular Hemoglobin (MCH) in pg, Mean Corpuscular Hemoglobin Concentration (MCHC) in g/dl, red cell distribution width (RDW%), Hemoglobin level (Hb) in g/dl and hematocrit percent (Hct%). Serum iron and ferritin were performed for patients and controls. Reference values for serum iron for children 35–167 µg/dl. Serum iron was assessed by a colormetric methods. Serum ferritin was done by enzyme-linked immunoassay (ELISA) by using IMX Ferritin assay which is also a MEIA for the quantitative determination of ferritin in human serum or plasma with reference values for children (22–293.3 mg/dl). At all ages a serum ferritin value of less than 10–12 pg/l (or ng/ml) indicates a depletion of iron stores.

**Iron intervention**

Oral iron supplementation in the form of ferrous sulfate (20% elemental iron by weight) with daily total dose of 6 mg/kg/day of elemental iron in 2–3 divided doses are given between meals.

**Follow up of Laboratory and anthropometric indices**

This was performed for all the cases every three months and for one year after starting iron therapy by measuring the blood indices Hb, Hct, MCV, MCH, and MCHC, and iron indices (serum iron, and serum ferritin) for the patient group and assessment of weight and height at each clinical visit by the same devices (at 0, 3, 6, 9, 12 months, not necessarily attending the whole visits; at least 3 visits are required including essentially the first and the last visits). For controls, sampling and anthropometric measurements were only done in the first and last visits.

**Statistical analysis**

Statistical Package for the Social Sciences (SPSS) software version 12.0 was used for data analysis. All anthropometric data were expressed in standard deviation score (SDS) applying the formula: (variable – mean) divided by 1 SD by using the software Growth Vision version 2 provided by Novo Nordisk Denmark. Data were presented as mean ± SD. For comparison of two groups Student’s t-test for dependent and independent variables was used. Chi-square test was used to compare qualitative variables. To compare two groups as regards quantitative and qualitative variables unpaired t-test and paired t-test were used respectively. Mann Whitney Willcoxon U and Willcoxon test were used instead of unpaired t-test and paired t-test in non-parametric data respectively. Linear Pearson’s correlation was also done. P-value is significant if <0.05.
Results

Eighty children; 40 children having IDA (aged 6 months to 5 years; 34 males and 6 females) with mean age (2 ± 0.8 years) were compared to a control group including 40 healthy clinically non-anemic, age and sex-matched subjects (mean age 2.7 ± 1.1 years; 25 males and 15 females). No statistically significant difference between both cases and control groups as regard age and gender, which means that the groups are homogeneous. No statistical significant difference between cases and controls as regards Target height SDS (−0.76 ± 0.9 and −0.46 ± 0.8 respectively) thus excluding familial short stature in both cases and controls groups.

Gradual improvement in the different anthropometric parameters including height SDS, weight SDS and BMI SDS, and the hematological parameters (including Hb, Hct, MCV, MCH, MCHC, RDW, serum iron and serum ferritin) was observed in the subsequent visits starting from the 2nd visit (at 3 months) to the last visit after the start of treatment with significant difference in comparison to the level before treatment (baseline visit) with a p-value of (<0.001) for each of these parameters. In addition, the percent of change in each subsequent visit (starting from the 2nd visit) was calculated in relation to the baseline visit (in which no treatment was given yet) in each subsequent visits (Table 1).

The height SDS, weight SDS, BMI SDS in baseline and last visits of the cases is significantly lower than those of the controls in the same visit with a P-value of (<0.001) for each parameter, but the difference is narrower (nearly no difference) in the last visit. Each of Hb levels, Hct, MCV, MCH, MCHC, RDW, serum ferritin and serum iron in baseline visit of the cases were significantly lower than those of the controls in the same visit with a P-value of (<0.001) for each. After treatment (in the last visit), no significant differences were found in MCHC, RDW, and serum iron between both groups with a p-value of (>0.05), however as regards Hct, MCH and serum ferritin the differences were narrower (nearly no difference) in the last visit with a P-value of (<0.05) for each (Table 2). No significant difference was detected between both cases and controls as regards MCV and Hb levels with a P-value of (>0.05) after treatment.

Comparing cases and controls as regards the growth velocity (GV) (one year height velocity) and GV SDS of cases were found significantly higher than controls (Table 3).

At the end of the study (last visit), a significant positive correlations between each of the height SDS and the Hb level and each of GV SDS and BMI SDS of the studied cases were found with a p-value (<0.001) for each (Figs. 1 and 2). Also, significant positive correlations between the serum ferritin level and each of GV SDS and BMI SDS of the studied cases after the treatment were detected with a p-value (<0.001) for each (Figs. 3 and 4).

Discussion

There is limited evidence available for the direct impact of iron therapy on anthropometric measures, which are essential to evaluate future benefits and effective strategies of iron supplementation. This study showed that iron is crucial for the growth of IDA infants and preschool children in Egypt.

On studying the different hematological parameters as indicators for iron deficiency anemia (IDA), it was found that there is

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### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (1st visit)</th>
<th>At 3 months (2nd visit)</th>
<th>At 6 months (3rd visit)</th>
<th>At 9 months (4th visit)</th>
<th>At 12 months (5th visit)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height SDS</td>
<td>−1.2 ± 0.3 (33%)</td>
<td>−0.84 ± 0.3 (33%)</td>
<td>−0.5 ± 0.2 (58%)</td>
<td>−0.29 ± 0.2 (75%)</td>
<td>−0.07 ± 0.2 (94%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight SDS</td>
<td>−1.08 ± 0.4 (10%)</td>
<td>−0.94 ± 0.3 (25%)</td>
<td>−0.79 ± 0.35 (25%)</td>
<td>−0.69 ± 0.38 (40%)</td>
<td>−0.53 ± 0.37 (53%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>0.3 ± 0.5 (22.4%)</td>
<td>0.4 ± 0.6 (35.9%)</td>
<td>0.5 ± 0.7 (38%)</td>
<td>0.6 ± 0.8 (38%)</td>
<td>0.7 ± 0.8 (25.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>8.6 ± 0.4 (22%)</td>
<td>9.9 ± 0.5 (23.6%)</td>
<td>10.6 ± 0.6 (23%)</td>
<td>10.8 ± 1.7 (23%)</td>
<td>11.8 ± 0.4 (33%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>27.9 ± 1.6 (15%)</td>
<td>31 ± 2.1 (18%)</td>
<td>32.3 ± 2 (22%)</td>
<td>33.7 ± 1.8 (22%)</td>
<td>34.7 ± 1.8 (26%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>64.5 ± 5 (15%)</td>
<td>68.2 ± 4 (13%)</td>
<td>72.2 ± 5 (15%)</td>
<td>74.5 ± 4 (15%)</td>
<td>76.7 ± 2.6 (19%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCH (pg)</td>
<td>20.3 ± 2.6 (10%)</td>
<td>22.3 ± 2.4 (21%)</td>
<td>24.5 ± 1.5 (25.5%)</td>
<td>25.1 ± 1.3 (25.5%)</td>
<td>26.6 ± 1.4 (25.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCHC (g/dl)</td>
<td>30 ± 1.3 (45%)</td>
<td>31.4 ± 1.4 (7.61%)</td>
<td>32.8 ± 0.9 (12.7%)</td>
<td>33.1 ± 2 (16.8%)</td>
<td>34.6 ± 1.4 (16.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>22.1 ± 2 (14.6%)</td>
<td>19.4 ± 2 (18%)</td>
<td>18 ± 2.6 (27.2%)</td>
<td>16.3 ± 1.6 (31.8%)</td>
<td>15.1 ± 1.2 (31.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum iron (µg/dl)</td>
<td>13.5 ± 6 (120%)</td>
<td>29.2 ± 13 (220.8%)</td>
<td>42.2 ± 20 (340%)</td>
<td>63 ± 31 (531.8%)</td>
<td>80.6 ± 31 (531.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum ferritin (pg/ml)</td>
<td>10.4 ± 3 (120.6%)</td>
<td>20.8 ± 10 (210.8%)</td>
<td>32.7 ± 10 (330.6%)</td>
<td>45.3 ± 14 (521.8%)</td>
<td>66.8 ± 31 (521.8%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All data are presented as mean ± standard deviation. P value <0.05 is significant.

% of change: the percent of change is calculated in relation to the first visit (in which no treatment was given yet) in each subsequent visit.

SD: standard deviation.

SDS: standard deviation score.

BMI: body mass index.

Hct: hematocrit percent.

Hb%: hemoglobin percent in gm/dl.

MCH: mean corpuscular hemoglobin in pg.

MCHC: mean corpuscular hemoglobin concentration in g/dl.

RDW%: red cell distribution width percent.
highly significant difference between subjects with IDA and controls as regard Hb, Hct, MCV, MCH and MCHC. Hb and MCV were shown in a previous study to be highly indicative for IDA. A significant improvement of all hematological values was found in our IDA patients after the start of iron therapy. These results were in agreement with several studies performed in different countries. This improvement in the hematological indices could be attributed to the more attention paid by the parents to the child's diet and health at home due to their awareness of the child's iron deficiency.

Serum ferritin, a storage protein, is a sensitive marker of iron storage. As iron stores diminish, the ferritin level falls. In IDA, as iron stores become depleted, the ferritin value will decrease. In our study, iron indices (serum iron, and serum ferritin) as indicators for IDA, were significantly lower in IDA subjects compared to the controls. Afifi and colleagues concluded the same finding, however, in another study it was found that serum ferritin is a sensitive marker of iron storage and as iron stores diminish, the ferritin level falls.

At baseline, a significant difference between the IDA patients and the controls was found regarding growth parameters such as height, height SDS, weight, weight SDS, BMI and BMI SDS with (P value < 0.001 for each). Several studies showed similar results which suggested that lower growth is an adverse effect of IDA in children and that iron supplementation improves both motor and physical development. Iron supplementation has been shown to significantly benefit weight and height of IDA children. In India, one study showed that the anthropometric parameters of the IDA children treated with iron were higher than that of anemic placebo treated children as shown by a better weight gain and a
Higher weight for height. Another study also reported that IDA caused poor growth in young infants due to the increased iron requirements. However, Chimonas and colleagues found that there is no difference between IDA subjects and controls as regard the different growth parameters, this may be explained by that they chose their patients in the stage of iron deficiency and the anemia didn't develop yet.

Significant improvement in all anthropometric parameters was shown in this study including; the height SDS, weight SDS, BMI and BMI SDS when comparing their values before treatment to their values one year after treatment and this was similarly concluded by Soliman et al. In our study, and after treatment with iron for 6 months, a significant acceleration of the IDA subjects' growth velocities were observed associated with improvement in their height SDS and there is a significant correlation between growth velocity (GV) and BMI on one hand and serum ferritin on the other hand. This agreed with results of a study by Carter et al. who concluded that there is an association between reduced weight and iron deficiency in these children. Similarly another study was conducted to detect the effect of oral iron supplementation on blood iron levels and physical growth and concluded that treatment with iron for 12 weeks resulted in a significant improvement in IDA subject's hematological status as well as GV. Also, it was reported that iron supplementation for 16 weeks had significant weight gain than the group received a placebo for similar duration. The differences among studies might be due to the difference in the duration of iron therapy or the different age groups selection. On the contrary, two more studies didn't document the positive effect of iron supplementation on the physical growth of IDA children. These studies are done in developing countries that have limited food availability and poor feeding, where improvement in the appetite of the child may not translate into increase energy intake, and therefore enhanced height gain. Also, another study reported that observational studies have postulated a positive effect on physical growth due to indirect effect of iron supplementation on the improvement in immunity leading to decreased incidence of infection and improvement in appetite and consequently the intake of energy.

One important observation of this study was the significant positive correlation between serum ferritin and both of GV SDS and BMI SDS, as well as a significant positive correlation between height SDS and each of Hb level and serum ferritin levels (after one year of treatment). Similarly, one study found that after treatment with iron for 6 months, the GV was correlated significantly with serum ferritin concentration and BMI. Also, Serum ferritin concentration was correlated significantly with BMI after iron therapy. Chwang et al. had also shown that hematological status, GV and morbidity levels improved significantly in IDA children receiving iron supplementation for 12 weeks. The World Health Organization conducted a study in Thailand which concluded that iron supplementation for 16 weeks had an effect on increasing height in elementary school age children. Iron supplementation was shown to significantly benefit weight for age and height for age parameters of IDA children. Perng and colleagues concluded that higher iron status, as indicated by ferritin and MCV, was related to slower linear growth in iron-replete school-age boys. This difference could be explained by the choice of different age groups; as this study selected school children while our subjects were mostly infants and preschool-aged children.

In summary, IDA during the first 5 years of life, when growth is fast, adversely affects both linear growth and weight gain which is reversible with iron therapy, thus adequate iron status is crucial for normal growth (both height and weight). The findings of the present study supported the beneficial effects of iron supplementation on physical growth parameters of IDA children.

To the best of our knowledge, this study is the first to examine the relationship of the growth velocity and iron status of pre-school children with IDA in Egypt by documenting the effects of this disease on growth at diagnosis, prior to the initiation of iron therapy and one year after the diagnosis.
Our study has some limitations because of limited information on the nutritional status at the initiation of the intervention and the duration of the intervention period evaluated also varied. As the iron nutritional status, especially serum ferritin may be altered by inflammation, therefore, inflammation indicators such as C-reactive protein should have been assessed which wasn’t performed in this study. Future studies are needed to identify the different endocrinologically and metabolic derangements associated with IDA and compromised growth. Additionally, future prospective population-based studies are necessary and must be performed at the national level.

Acknowledgment

We thank all subjects and parents who participated in our study. We would like to express our appreciation to our colleagues and nurses at DEMPU and the Pediatric Hematology Clinic who facilitated this work.

References


