Brief Report
Linear Growth in Children with Iron Deficiency Anemia Before and After Treatment

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Summary
We measured growth (length (L) standard deviation score (SDS), growth velocity (GV) SDS and body mass index (BMI]) and hematological (hemoglobin, hematocrit, MCV and MCH) parameters in 40 children (aged 17.2 ± 12.4 months) with iron deficiency anemia (IDA) before and after iron therapy. Before treatment children with IDA had LSDS = −1.2 ± 1, GV = 7.5 ± 2.2, GVSDS = −1.42 ± 0.6 and BMI = 13.5 ± 1.2. They were significantly shorter and had reduced growth as compared with age-matched controls. After treatment, their growth parameters significantly increased with LSDS = −0.6 ± 0.9, GV = 13.2 ± 4.4 cm year⁻¹, GVSDS = 1.7 ± 0.5 and BMI = 14.2 ± 1.1. Their GV correlated significantly with serum ferritin concentration (r = 0.48, p < 0.001) and BMI (r = 0.32, p < 0.1). In summary, IDA during the first 2 years of life significantly impairs growth.

Key words: iron deficiency, anemia, growth.

Introduction
Iron deficiency is the most common nutritional deficiency worldwide particularly affecting infants and children [1, 2]. Iron is vital for all living organisms because it is essential for multiple metabolic processes, including oxygen transport, DNA synthesis and electron transport [1]. Infancy is the critical period for linear and brain growth, and nutrient deficiencies during this time may affect both growth potential and psychomotor development.

There is still controversy over whether iron supplements result in increased growth [3–5], decreased growth [6] or no effect on growth [7–9] in young children. Similarly, there is still a debate about the possibility that iron supplements or iron-fortified foods may increase the incidence of certain types of infections, particularly gastrointestinal infections [10]. The degree of growth retardation at presentation, if any, and the magnitude of catch-up growth and their relationship to the changes in hematologic parameters and the effect of iron treatment on the total differential leucocyte count needs further clarification.

Objectives
(1) To determine the degree of linear growth retardation of infants and young children with iron deficiency anemia (IDA) at presentation.
(2) To measure growth parameters for 6 months or more after treatment with iron for 3 months.
(3) To correlate the RBC indices with different growth parameters.
(4) To measure the changes, if any, in the total and differential white cell count after treatment with iron.

Patients and Methods
In this prospective study, infants and children < 4 years of age (n = 40) with IDA attending the Pediatric Clinic at Hamad Medical Centre, Doha, Qatar, between 1 January 2006 and 31 December 2006 were randomly selected and studied. Forty healthy clinically nonanemic, age- and sex-matched children were used as controls for the anthropometric data.

Patients’ inclusion criteria included clinical manifestations of anemia with:
(1) low hemoglobin (Hb) (<10 gm dl⁻¹)
(2) low hematocrit (Hct) (<33%)
(3) microcytic hypochromic picture in the blood film
(4) low serum ferritin (<10)

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Results of lab investigations collected from the patients’ files prior to and 3–6 months after treatment with oral iron included:

(1) complete blood count including blood smear
(2) serum electrolytes (Na, K, Ca, PO₄)
(3) serum creatinine
(4) serum alanine transferase and alkaline phosphatase

Exclusion criteria

(1) Infants/children with past history of prematurity or of having been born small for date.
(2) Infants/children with chronic systemic illnesses, protein/calorie malnutrition, rickets, malabsorption, liver disease, renal insufficiency or other forms of anemia.

The protocol of the study was approved by the Research Ethics Committee at Hamad Medical Centre, Doha, Qatar before the beginning of the study.

All patients were examined thoroughly with special reference to the following:

(1) Detailed history taking including nutritional intake.
(2) Physical examination including clinical manifestations of IDA.
(3) Anthropometric measurements including weight and height.
(4) The Height standard deviation score (HtSDS) and body mass index (BMI) were calculated. Normal population reference data were according to Tanner et al. Annualized growth velocity (GV) was calculated by measuring the growth rate in length/height for at least 4 month after initiation of iron therapy. Normal growth data were according to Tanner et al. [10].
(5) Complete blood count, RBC indices and serum ferritin concentrations were performed before the beginning of treatment and every 3 months for 6 months.

Statistical analysis

Results are expressed as the mean ± SD and analyzed by paired student t-test to compare growth parameters and analyte concentrations before vs. after treatment. A nonpaired student t-test was used to compare patients with age- and sex-matched control group. Correlations between variables of interest were examined by linear regression analyses.

Results

At presentation, patients with iron deficiency had low Hb (8.2 ± 1.2 g dL⁻¹), Hct (29 ± 2.8), MCV (61.5 ± 8.1) and MCH (19 ± 3.2) which improved significantly after treatment (11.2 ± 1.2 g dL⁻¹, 70.6 ± 6.8, 23.4 ± 2.9 and 18.9 ± 5, respectively).

Before treatment children with iron deficiency had length standard deviation score (LSDS) = –0.6 ± 0.2, annualized GV = 7.5 ± 2.2 cm year⁻¹, GV standard deviation score GVSDS = –1.42 ± 0.6 and BMI = 13.5 ± 1.2. They were significantly shorter and growing slowly compared to age-matched controls (Table 1).

### Table 1

<table>
<thead>
<tr>
<th>Growth and hematological data of patients and controls</th>
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<tbody>
<tr>
<td>Patients Before treatment After 6 months Controls</td>
</tr>
<tr>
<td>Number</td>
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<tr>
<td>Age (months)</td>
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<tr>
<td>HtSDS</td>
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<tr>
<td>BMI</td>
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<tr>
<td>GV (cm year⁻¹)</td>
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<td>GVSDS</td>
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<td>MCV (fL)</td>
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<td>MCH (pg)</td>
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<td>Ferritin (mcg L⁻¹)</td>
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<td>Total WBC (1000 cmm⁻¹)</td>
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<td>Neutrophils (1000 cmm⁻¹)</td>
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<td>Lymphocytes (1000 cmm⁻¹)</td>
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<td>Platelets (1000 cmm⁻¹)</td>
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*p < 0.05 before vs. after treatment.

**p < 0.01 patients vs. controls.

NA = not available.
After treatment for 6 months and correction of the anemia, their growth parameters significantly increased with $\text{LSDS} = -0.6 \pm 0.9$, annualized $\text{GV} = 13.2 \pm 4.4 \text{cm year}^{-1}$, $\text{GVSDS} = 1.7 \pm 0.5$ and $\text{BMI} = 14.2 \pm 1.1$). These growth data clearly indicated significant weight gain and accelerated linear growth associated with correction of their hematological parameters.

After treatment with iron for 6 months, the GV was correlated significantly with serum ferritin concentration ($r = 0.48$, $p < 0.001$) and BMI ($r = 0.32$, $p < 0.1$). Serum ferritin concentration was correlated significantly with BMI after iron therapy ($r = 0.402$, $p < 0.001$).

The total leucocytic and lymphocytic counts did not differ before vs. after treatment but there was a significant decrease in the neutrophil and platelet counts after vs. before treatment.

**Discussion**

Iron deficiency is the most prevalent nutritional deficiency in the world, and iron deficiency and its anemia affect more than 3.5 billion people in the developing world [11]. IDA decreases oxygen carrying capacity and further compromises energy production [12, 13]. Consequences of iron deficiency and anemia include: prematurity and low birth weight, impaired physical growth and neurocognitive function in children [11]. During the first months of life, the newborn rapidly utilizes iron stores due to an accelerated growth rate and commensurate increased blood volume. Maternally derived iron stores are generally sufficient for the first 4–6 months; however, sustained growth demands an increased iron supply. By the end of the second year of life, the child’s growth rate decreases but still faster than the rest of the childhood period and accompanying iron needs are still comparatively high. There is still controversy over the effect of iron supplements on linear growth [3–9].

Three stages of iron deficiency have been described. The initial stage, iron depletion, occurs when stored iron in the bone marrow diminishes due to insufficient supply of iron. Generally this stage is asymptomatic, creates no overt effect on erythropoiesis and escapes detection by Hb or Hct screening. Continued iron store depletion leads to the second stage, iron deficiency, during which storage levels become substantially reduced and Hb synthesis begins to be affected. The final stage, IDA, develops when iron stores are insufficient to maintain Hb production. This advanced stage will be reflected in low Hb and Hct values. It is important for the practitioner to understand that by the time low Hb or Hct levels are discovered on routine screening, the iron stores have been significantly depleted and will need replenishment [14, 15] 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 [14, 16].

In this study, 40 toddlers with IDA were significantly shorter with markedly slower growth velocity at presentation compared to age- and sex-matched normal controls ($p < 0.01$). After treatment with iron for 3 months, a significant acceleration of their growth velocity was observed associated with improvement in their LSDS. These findings confirmed that iron deficiency causes delayed growth in stature and weight which is reversible with iron therapy [4, 5].

After treatment, the significant correlation between growth velocity and BMI on the one hand and serum ferritin on the other hand suggests that the iron status is important for normal growth in length and weight. In the replete state, children grow better compared to growth during the deplete state. These 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 [1]. Iron–sulfur clusters are crucial cofactors of numerous proteins involved in enzyme catalysis, electron transport and regulation of gene expression [17, 18].

In addition, iron deficiency may affect growth through IGF-I dependent mechanism. It was shown that IGF-I concentration has important relationship to iron metabolism and protoporphyrin synthesis in children and adolescents [19].

Because neutrophils have many iron-containing compounds, including myeloperoxidase and cytochrome, the occurrence of neutropenia and lymphopenia in iron-deficient animals [20–23] and humans [24, 25] may be due to the adverse effect of iron deficiency on many parameters of humoral, cell-mediated and nonspecific immunity and the activity of cytokines [26]. In this study, the total white cell, lymphocyte and neutrophil counts were not reduced during iron deficiency. The significant reduction of the total neutrophil and platelet counts with treatment was also previously reported [24].

In summary, IDA during the first 2 years of life, when growth is fast, adversely affects both linear growth and weight gain. The mechanisms of defective growth IDA are still unclear and need further studies.


