Iron Deficiency Anaemia in Jamaican Children, Aged 1–5 Years, with Sickle Cell Disease

L King¹, M Reid¹, TE Forrester¹

ABSTRACT

Objective: The aim of this study was to determine, using a combination of measures, the prevalence of iron deficiency anaemia (IDA) in children under five years-of-age who have sickle cell disease (SCD) and attend the Sickle Cell Clinic (SCU) of the Tropical Medicine Research Institute.

Materials and Methods: Children with homozygous sickle cell anaemia (Hb SS) or doubly heterozygous for Hb S and Hb C (Hb SC) disease who had not received a blood transfusion within three months prior to the iron measurements, were enrolled. The diagnosis of IDA was made if transferrin saturation was less than 16% with serum iron less than 10.7 µmol/l and a low mean corpuscular volume (MCV) for age.

Results: Twelve children (8.5%), seven with Hb SS and five with Hb SC had IDA. Adjusting for genotype, children with IDA had significantly higher red blood cell (RBC) counts (4.3 x10⁹/l vs 3.0 x 10⁹/l, p < 0.001) and total iron binding capacity (TIBC) (65.6 µmol/l vs 55.2 µmol/l, p < 0.004) but significantly lower reticulocyte (retic) counts (7.8 % vs 12.2%, p = 0.001) than children without IDA.

Conclusion: Iron deficiency anaemia is a clinical problem which affects children with SCD in Jamaica. The higher RBC counts in the IDA group may be due to decreased haemolysis and increased red cell survival whilst the lower reticulocyte counts may be due to impaired erythropoiesis. These observations need to be extended by clinical studies to establish improved diagnostic measures for IDA in SCD. Additionally, clinical trials are needed to determine whether treatment of IDA in children with SCD reduces morbidity and is associated with clinical benefits such as improvements in neurocognitive function.

Anemia por Deficiencia de Hierro en los Niños Jamaicanos Entre 1 y 5 Años de Edad, que Padecen la Enfermedad de Células Falciformes

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RESUMEN

Objetivo. El objetivo de este estudio fue determinar – mediante una combinación de medidas – la prevalencia de anemia por deficiencia de hierro (ADH) en niños menores de cinco años de edad que padecen la enfermedad de células falciformes (ECF), y asisten a la Clínica de Células Falciformes (CCF) del Instituto de Investigación de Medicina Tropical.

Materiales y métodos. Se inscribieron niños con anemia de células falciformes homocigóticas (Hb SS) o enfermedad doble heterocigoto por Hb S y Hb C (Hb SC), que no habían recibido transfusión de sangre por un periodo de tres meses antes de las mediciones de hierro. Se diagnosticaba ADH si la saturación de la transferrina era menos del 16%, con hierro en suero inferior a 10.7 mol/l, y un volumen corpuscular medio (VCM) bajo para la edad.

Resultados. Doce niños (8.5%), siete con Hb SS y cinco con Hb SC presentaban ADH, después del ajuste de las diferencias en el genotipo, los niños con ADH tuvieron conteos de glóbulos rojos (RBC) (4.3 x10⁹/l vs 3.0 x 10⁹/l, p < 0.001), y capacidad total de fijación del hierro (TIBC) (65.6 µmol/l vs 55.2 µmol/l, p < 0.004) significativamente más altos, pero conteos de reticulocitos (7.8% vs 12.2%, p = 0.001) significativamente más bajos que los niños sin ADH.

Conclusión. La anemia por deficiencia de hierro es un problema clínico que afecta a los niños con ECF en Jamaica. El hecho de que los conteos de RBC sean más altos en los grupos con ADH, puede
INTRODUCTION
Iron deficiency is one of the most common nutritional deficiencies worldwide and is the leading cause of anaemia, especially in children and adult women (1, 2). Children in the developing world are especially vulnerable because of the increased requirements of growth (3), high helminth burden (2, 4) and diets with low iron bioavailability (2). In Jamaica, the prevalence of iron deficiency anaemia (IDA) in children is estimated at about 30% (5).

In sickle cell disease (SCD), the chronic haemolysis characteristic of the disorder results in an increased availability of iron from red cell destruction. Additionally, the reported increase in absorption of iron from the gastrointestinal tract (6) as well as the iron provided by blood transfusions (7, 8) would suggest that iron deficiency is unlikely in SCD. Indeed, Serjeant et al (9) have reported that serum iron levels were significantly higher in young children with Hb SS than in controls, standardized for age and gender. However, in contrast to these findings Rao et al (10) and Vichinsky et al (11) using different criteria have reported cases of IDA in SCD with prevalence of 12% and 8% respectively. The identification of IDA in children with SCD is important, as IDA contributes to worsening of anaemia (11) and may have negative long-term consequences on neurological development (12, 13) and growth (3).

The diagnosis of iron deficiency is based primarily on laboratory measurements. However, conventional tests used, mean corpuscular volume (MCV), transferrin saturation and serum ferritin are limited because of varying ranges of sensitivities and specificities, as they may be modified by conditions other than iron deficiency such as age (14), chronic inflammation (15), genetic polymorphism (16) and by SCD (11, 17, 18). Current literature suggests that a low MCV for age, transferrin saturation less than 16% and serum ferritin less than 25 ng/ml are each 100% sensitive for IDA in SCD (10, 11). On the other hand, whilst serum ferritin less than 25 ng/ml is 100% specific for IDA in SCD, transferrin less than 16% and low MCV for age have specificities of 77–87% and 97% respectively (10, 11). Thus, it has been proposed that the use of a battery of tests to define iron status in a population improves precision in diagnosis of IDA. At the Sickle Cell Unit (SCU) in Jamaica, iron status is determined by the use of iron study tests: MCV, serum iron, total iron-binding capacity (TIBC) and transferrin saturation. Using this battery of tests, we sought to determine the prevalence of IDA in children under five years-of-age attending the SCU, and to describe differences between the IDA and non-IDA groups in terms of anthropometric and haematological variables.

MATERIALS AND METHODS
The sample consisted of children under five years-of-age with homozygous sickle cell anaemia (Hb SS) or doubly heterozygous for Hb S and Hb C (Hb SC) disease who attended the SCU during a two-year period (November 2001 – November 2003) and had iron measurements performed. Iron measurements are performed at the SCU on the initial visits of new patients and on clinical suspicion of IDA. Children who received a blood transfusion within three months prior to the iron measurements were excluded from the study. One hundred and forty-one children: 121 with Hb SS and 20 with Hb SC disease satisfied the study criteria.

The diagnosis of SCD was determined by Hb electrophoresis on cellulose acetate, pH 8.4, and citrate agar, pH 6.2. Quantitative HbA₂ levels by cellulose acetate membrane and HbF by Betke method confirmed the diagnosis. The haematological variables – haemoglobin (Hb), nucleated blood cell (NBC) count, platelet count (plts), red blood cell (RBC) count, and MCV, were determined using a Coulter MAX-M. Reticulocyte counts (retics) were performed by tube test method (staining technique). Serum iron and iron-binding capacity (TIBC) were determined using an Abbott Alycon autoanalyser. Transferrin saturation was calculated from serum iron and TIBC. The child was classified as having IDA if all three criteria: transferrin saturation less than 16%, serum iron less than 10.7 µmol/l, low MCV for age: 0.5–2 yr < 70 fl, 2–5 yr < 73 fl (19) were present. Cut-off points were based on laboratory standards as well as other studies (10, 11). Height and weight measurements performed at the time of iron measurements were recorded and body mass index (BMI) calculated.

Statistics
Values are expressed as means ± sd. Differences in mean values between the IDA group and the non-IDA group adjusting for genotype effects were determined by ordinary linear regressions. The Stata statistical package version 8 for Windows™ (Stata Corporation, College Station, TX) was used for data-analysis.

RESULTS
Using our IDA criteria, 12 children, seven with Hb SS and five with Hb SC had IDA resulting in a prevalence of 8.5%. There was a significantly greater than expected prevalence in...
patients with Hb SC (42%) vs Hb SS (5.8%). The distributions of serum iron concentration and transferrin saturation were skewed to the right with median, minimum and maximum values being 9.7 µmol/l, 0.2 µmol/l, 40.7 µmol/l and 18%, 1%, 71% respectively (Figure). In contrast, the distribution of MCV for the total sample was left skewed with median, minimum and maximum values being 83 fl, 57 fl and 102 fl respectively (Figure).

The anthropometric characteristics of the IDA and non-IDA groups are shown in Table 1. There was no significant difference in the means of the anthropometric variables between the two groups. The haemoglobin concentration ranged from 5.5 g/dl to 12.1 g/dl with a mean of 9.3 g/dl in the IDA group and from 5.6 g/dl to 11.4 g/dl with a mean of 8.3 g/dl in the non-IDA group (Table 2). This difference (9.3 g/dl vs 8.3 g/dl) in mean values was statistically significant (p < 0.03). As expected, patients with Hb SC had significantly higher Hb (~ 2gm/dl) than did patients with Hb SS, this being independent of IDA status. However, in a regression model with haemoglobin concentration as the outcome variable and IDA status and genotype entered simultaneously as independent categorical factors there was no significant difference in mean haemoglobin concentration of IDA groups, adjusting for genotype (Table 2).

Children with IDA also had significantly higher RBC counts (4.3 x10⁹/l vs 3.0 x 10⁹/l, p < 0.001) and TIBC (65.6 µmol/l vs 55.2 µmol/l, p < 0.004) than children without IDA, independent of genotype (Table 2). On the other hand, reticulocyte counts were significantly lower in the children with IDA than in children in non-IDA group (7.8% vs 12.2%, p = 0.001), this difference also being independent of genotype (Table 2).

Compared to the tri-test measure for the diagnosis of IDA in this study, each individual criterion was as sensitive but specificity varied from 46% to 64% (Table 3). Low MCV for age had the best test performance characteristics and serum iron the worst.

DISCUSSION

In this cross-sectional study, a battery of tests was used in order to increase the specificity in diagnosing IDA. Using these tests, data demonstrated that of the 141 children with Hb SS and Hb SC who had had serum iron determination within the last two years at the SCU, 8.5% of children tested would be considered to have IDA. The data further demonstrate that there were significant differences in haematological and biochemical indices with RBC counts (p < 0.001) and TIBC (p < 0.004) being significantly higher in the IDA group versus the non-IDA group. On the other hand, reticu-
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Table 2: Haematological variables by genotype and IDA group

<table>
<thead>
<tr>
<th>Variables</th>
<th>SC</th>
<th>IDA</th>
<th>Non-IDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)†</td>
<td>10</td>
<td>8.4</td>
<td>8.1</td>
</tr>
<tr>
<td>NBC (x 10^9/l)†</td>
<td>10</td>
<td>4.8</td>
<td>7.1</td>
</tr>
<tr>
<td>RBC (x 10^12/l)†</td>
<td>285.4</td>
<td>386.9</td>
<td>390.4</td>
</tr>
<tr>
<td>Plts (x 10^9/l)</td>
<td>285.4</td>
<td>386.9</td>
<td>390.4</td>
</tr>
<tr>
<td>Retics (%) †</td>
<td>6.4</td>
<td>8.7</td>
<td>7.1</td>
</tr>
<tr>
<td>TIBC (µmol/l)</td>
<td>63.1</td>
<td>67.4</td>
<td>57.4</td>
</tr>
</tbody>
</table>

Values are mean (sd). Abbreviations: TIBC – total iron binding capacity; Hb- haemoglobin; RBC – red blood cells; Plts– platelets; NBC – nucleated blood cells; Retics – reticulocytes. † effect of genotype p < 0.05; * p < 0.004, ** p < 0.001 comparing means for IDA group vs non-IDA group, adjusting for genotype effects.

Table 3: Test Performance characteristic of individual criterion for diagnosing iron deficiency anaemia in young children with sickle cell disease compared with the tri-test criteria.

<table>
<thead>
<tr>
<th>Transferrin saturation criterion</th>
<th>Serum Iron criterion</th>
<th>Low MCV age criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity %</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Specificity %</td>
<td>64.3</td>
<td>46</td>
</tr>
<tr>
<td>Positive Predictive Value %</td>
<td>20.7</td>
<td>14.6</td>
</tr>
<tr>
<td>Likelihood ratio positive</td>
<td>2.8</td>
<td>1.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21.5</td>
</tr>
</tbody>
</table>

Sensitivity is the proportion of diseased patients correctly identified. Specificity is the proportion of healthy patients correctly identified. The positive predictive value (PPV) is the probability of a patient having the disease following an abnormal test result assuming a prevalence of 8.5%. The likelihood ratio of a positive test is the ratio of the probability (likelihood) of a positive test result in an abnormal patient and in a normal patient = Sensitivity/(1- specificity).

RBC (x 10^12/l) † 4.6 (0.3) 4 (0.9) 4.3 (0.8)** 3.9 (0.4) 2.9 (0.6) 3 (0.7)

Whether the reduction in haemolysis and increased red cell survival associated with IDA in SCD is accompanied by clinical benefit is unclear (27). Clinically, there is evidence
that IDA contributes to worsening of anaemia (11) and has negative long-term consequences on neurocognitive development (12, 13), especially if it develops during early childhood. Children with SCD have impaired neurocognitive development from various postulated factors including cerebrovascular accidents (CVAs) – clinical CVAs and silent infarcts (29), an encephalopathic process (30), and chronic anaemia (31). It can therefore be argued that development of IDA in children with SCD would exacerbate neurocognitive impairment. Additionally, IDA is associated with impaired growth (3) and this may further worsen the growth deficit observed in SCD (32).

In summary, IDA is a clinical problem, which affects children with SCD in Jamaica. However, the highly selective nature of the sample requires one to exercise caution in generalizing the findings of this study. Nonetheless, these observations need to be extended by clinical studies to establish improved diagnostic measures of IDA in SCD and further to determine whether treatment of IDA reduces morbidity and improves neurocognitive development in children with SCD.

REFERENCES