

## EFFECT OF MALARIA ON SOLUBLE TRANSFERRIN RECEPTOR LEVELS IN TANZANIAN INFANTS

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**Abstract.** The diagnosis of iron deficiency anemia in malaria endemic areas is complicated by the influence of the infection on the laboratory tests conventionally used to assess iron status. Determination of soluble transferrin receptor (sTfR) levels has been shown to be a sensitive indicator of iron deficiency in adults and is not affected by a range of infectious and inflammatory conditions. The utility of sTfR levels in the diagnosis of iron deficiency in malaria endemic areas remains unresolved.

Three hundred and fourteen infants in a rural area of southern Tanzania living under conditions of intense and perennial malaria transmission were studied to determine the utility of sTfR plasma levels in the assessment of iron deficiency anemia. Independent of the presence of anemia, malaria parasitemia was associated with a significant increase in sTfR plasma levels that were even higher than those found in iron deficiency anemia. We conclude that the measurement of sTfR levels does not have a role in the diagnosis of iron deficiency anemia in young children exposed to malaria infection.

### INTRODUCTION

Iron deficiency is the most common cause of anemia and the most prevalent nutritional problem worldwide.<sup>1</sup> Iron deficiency anemia is especially common in developing regions where infants, young children, and pregnant women are particularly at risk. Malaria infection is another major cause of anemia affecting the same populations. The geographic distribution of iron deficiency anemia and malaria transmission often overlap. Malaria infection affects the conventional laboratory tests of iron status such as plasma iron, ferritin, total iron binding capacity (TIBC) and transferrin saturation.<sup>2</sup> Because of hemolysis, plasma iron may be also increased in malaria infection.<sup>3</sup> Due to the complexity in the interpretation and the lack of specificity of the available tests for iron status determination, the clinical management of the anemic patient in malarious areas usually includes an empiric combination of treatments for anemia aimed at the most common causes. This influences the quality of health care as well as having important economic implications for the health sector. In the absence of definitive confirmation of iron deficiency through bone marrow examination, there is a need for non-invasive and specific tests especially in areas where iron deficiency is highly prevalent.

Together with ferritin concentration, soluble transferrin receptor (sTfR) serum levels have been suggested to be sensitive indicators of iron status in adults.<sup>4</sup> Unlike other laboratory tests of iron status (such as plasma ferritin, iron, TIBC, and transferrin saturation), sTfR levels are not affected by infectious or inflammatory conditions, or pregnancy, in the absence of iron deficiency.<sup>5</sup> In recent years the determination of sTfR levels has been proposed as a useful new tool in the diagnosis of iron deficiency in anemic patients.<sup>5</sup> Serum levels of sTfR were increased in anemic adult patients with iron deficiency either with or without an associated inflammatory condition, while they were within the normal range in those with chronic infectious or inflammatory diseases alone.<sup>6</sup>

There have been very few reports on the usefulness of

sTfR levels in the diagnosis of iron deficiency in children<sup>7</sup> and only two from malaria endemic areas. These studies had contradictory results.<sup>8,9</sup> One suggested that sTfR levels were not affected by malaria;<sup>8</sup> the other observed that sTfR levels were significantly lower.<sup>9</sup> Differences in the prevalence of iron deficiency and hemoglobinopathies, malaria endemicity and the age groups of the individuals studied were proposed to account for these discrepancies. Neither of these studies focused on infants, the group most affected by both iron deficiency and malaria anemia in highly endemic areas.<sup>10,11</sup> We have therefore investigated the usefulness of sTfR levels in infants exposed to intense malaria transmission to assess iron deficiency anemia. These infants were originally enrolled into an intervention trial for the prevention of malaria and anemia.

### MATERIALS AND METHODS

**Study area and population.** The study took place in the town of Ifakara, Kilombero district in southeastern Tanzania. The demographic characteristics and malaria epidemiology of the area have been described in detail elsewhere.<sup>12</sup> In brief, malaria transmission is intense and perennial with an estimated entomological inoculation rate (EIR) of 300 infective bites per person per year in a nearby village.<sup>13</sup> Clinical malaria is one of the main causes of hospital admission in children, the majority of cases and deaths occurring in individuals less than 1 year of age.<sup>11</sup> Of the admitted children, 35% of those less than 5 years old and 41% of those less than 1 year of age had moderate or severe anemia (Menendez C and others, unpublished data). A recent intervention study carried out in this area identified malaria as responsible for about 60% of severe anemia episodes (packed cell volume [PCV] < 25%) in infants; iron deficiency accounted for about 30% of such episodes.<sup>14</sup>

**Study design and definitions.** The current study was part of a randomized placebo-controlled trial of malaria chemoprophylaxis and iron supplementation for the prevention of

TABLE 1  
Definitions

Clinical malaria	<i>Plasmodium falciparum</i> parasitemia of any density and axillary temperature $\geq 37.5^{\circ}\text{C}$
Asymptomatic malaria	<i>P. falciparum</i> parasitemia of any density with an axillary temperature $< 37.5^{\circ}\text{C}$
Iron deficiency	<i>Plasma ferritin</i> $< 10$ (ng/mL) and/or Plasma iron $< 11$ ( $\mu\text{g/dL}$ ) and Plasma transferrin concentration $> 347$ (mg/dL)
Anemia	PCV $< 33\%$
Inflammation	C-reactive protein (CRP) $> 0.8$ mg/dl
Microcytosis	Mean corpuscular volume (MCV) $< 70$ fl

malaria and anemia in infants. Children were randomized at two months of age to receive iron supplements, malarial chemoprophylaxis or placebo for 4 and 10 months respectively.<sup>14</sup> Soluble transferrin receptor levels were measured in 314 randomly selected infants of the 611 (51%) who were visited at 8 months of age. At this visit, finger prick blood samples were collected for hematological, biochemical and parasitological analysis. Definitions used in the study are presented in Table 1.

Informed consent was obtained from all parents or guardians of the study infants. The study received ethical clearance from the Tanzanian Commission for Science and Technology and from the Ethical Committee of the Hospital Clinic in Barcelona.

**Laboratory procedures.** Blood samples were collected into EDTA and heparin microtainers (Becton Dickinson) and the separated plasma stored at  $-20^{\circ}\text{C}$ . Plasma soluble transferrin receptor levels were measured by an enzyme immunoassay using a kit from Orion Diagnostica (Espoo, Finland); according to the manufacturer the 25<sup>th</sup> and 97.5<sup>th</sup> percentiles of the reference distribution range for the kit were 1.3 and 3.3 mg/L respectively. Plasma ferritin was measured by a radioimmunoassay (Tandem-R Ferritin, Hybritech Inc, San Diego, CA); for the kit, the normal range for children of this age was 10–83 ng/mL. Plasma iron (reference range 11–150  $\mu\text{g/dl}$ ) was measured colorimetrically using the ferrozine method without deproteinization (Roche Diagnostics, Basel, Switzerland) in a Cobas Mira S analyzer. Plasma transferrin (reference range 218–347 mg/dl) and C-reactive protein were assayed by immunonephelometric methods (Dade Behring, Marburg, Germany).

Blood counts, hemoglobin (Hb), PCV, and the mean corpuscular volume (MCV) were determined on a semiautomatic cell counter (Sysmex F800 microcell counter, TOA Medical Electronics, Kobe, Japan).

Thick and thin blood films were stained and read for malaria parasites following standard, quality-controlled procedures.<sup>12</sup> Hemoglobin electrophoresis was performed on cellulose acetate strips.

**Statistical methods.** Variables were compared between the anemia groups using regression analysis. The model was adjusted for the treatment groups. Spearman's test was used for correlation analysis. Student's *t*-test was used to compare MCV values. Logarithmic transformation was done for variables that were not normally distributed: PCV, ferritin, iron, transferrin concentration, sTfR, and C-reactive protein and

TABLE 2  
Prevalence of hematologic and parasitologic variables in study children at 8 months of age

	n/N (%)
Hb Genotype AS	39/125 (31.2)
Malaria parasitemia*	48/314 (15.3)
Iron deficiency†	37/314 (11.8)
Anemia (PCV $< 33\%$ )	145/312 (46.5)
Inflammation (CRP $> 0.8$ mg/dL)	98/305 (32.1)
Microcytosis (MCV $< 70$ fl)	132/284 (46.5)

\* Asexual *Plasmodium falciparum*.

† Plasma ferritin  $< 10$  (ng/mL) and/or Plasma iron  $< 11$  ( $\mu\text{g/dL}$ ) and Plasma transferrin concentration  $> 347$  (mg/dL).

PCV = packed cell volume; MCV = mean corpuscular volume; CRP = C-reactive protein.

parasite density. Statistical analysis was done using Stata Statistical Software version 5.0 (Stata Corporation, College Station, TX).

## RESULTS

Children were grouped according to the presence of anemia, iron deficiency, and malaria. Infants in group I (control group) did not have anemia, iron deficiency, or malaria ( $n = 142$ ); group II were those with anemia alone ( $n = 86$ ); group III had iron deficiency anemia (IDA) (but not malaria) ( $n = 25$ ); and group IV had anemia plus malaria (but not iron deficiency) ( $n = 34$ ). The remaining 27 infants in whom sTfR levels were measured belonged to two or more categories; that is, they were either anemic or not anemic with iron deficiency and malaria.

Hemoglobin genotype results were available in 125 children of whom 39 (31.2%) had the genotype AS (this prevalence is higher than that previously reported from the area<sup>14</sup> and it is probably due to chance variation in the selection of the sample). Soluble transferrin receptor levels did not differ significantly by sex, presence of fever, microcytosis or Hb genotype (Menendez C and others, unpublished data). For this reason, analysis was done without distinction between these variables.

Hematological and parasitological features of the study population are shown in Table 2. The geometric mean sTfR level in the overall sample of children was 4.1 ng/ml (95%CI: 3.9–4.3). STfR levels correlated directly with transferrin concentration ( $r = 0.35$ ;  $P < 0.001$ ) and inversely with PCV ( $r = -0.40$ ;  $P < 0.001$ ) and iron ( $r = -0.10$ ), although the latter correlation was of borderline significance ( $P = 0.07$ ). There was also a direct and significant correlation with the density of parasitemia ( $r = 0.36$ ;  $P < 0.001$ ). When compared with the control group, mean geometric sTfR levels were significantly higher in non-anemic children who had malaria infection (3.4 [95%CI: 3.2–3.6] versus 5.4 [95%CI: 3.9–7.6];  $P < 0.001$ ).

Hematological parameters (PCV and MCV), ferritin, iron, transferrin concentration, C-reactive protein, and sTfR were compared between the different categories of anemia using multiple regression analysis adjusting for the treatment group (Table 3). Mean sTfR concentrations were significantly lower in all intervention groups compared to the placebo group (Menendez C and others, data not shown). The analysis showed that both IDA and malaria-anemia were in-

TABLE 3  
Hematologic and biochemical parameters in the study infants by anemia group

	Group I (Control)	Group II (Anemia alone)	Group III (IDA)	Group IV (Malarial-anemia)	Miscellaneous group
PCV (%)†	36.9 (36.2, 37.6)	30.0*** (29.4, 30.6)	29.9*** (29.1, 30.7)	27.1*** (25.8, 28.4)	36.4 (35.3, 37.5)
MCV (fL)‡	72.1 (6.7)	69.6* (6.6)	65.4** (7.6)	71.4 (7.1)	71.8 (7.4)
Plasma iron (µg/dL)†	37.9 (35.0, 41.1)	35.2 (31.8, 39.1)	23.9*** (18.3, 31.3)	38.5 (30.7, 48.3)	37.8 (30.1, 47.6)
Plasma ferritin (ng/mL)†	37.6 (33.1, 42.8)	35.7 (29.6, 43.0)	8.1*** (5.9, 11.2)	62.7*** (43.6, 90.2)	23.1* (13.5, 39.7)
Plasma transferrin concentration (mg/dL)†	322.5 (313.9, 331.3)	326.5 (316.2, 337.2)	376.0*** (361.4, 391.3)	355.0** (336.4, 374.6)	358.0** (342.8, 373.7)
C-reactive protein (mg/dL)†	0.7 (0.6, 0.8)	0.8 (0.7, 0.9)	0.7 (0.5, 1.0)	1.5*** (1.0, 2.3)	0.8 (0.6, 1.1)
sTfR (ng/mL)†	3.4 (3.2, 3.6)	4.2** (3.8, 4.6)	5.4*** (4.6, 6.3)	6.8*** (5.8, 7.9)	4.5** (3.8, 5.4)

PCV = packed cell volume; MCV = mean corpuscular volume; sTfR = soluble transferrin receptor; anemia = PCV < 33%; IDA = iron deficiency anemia; miscellaneous group = anemic or non-anemic with iron deficiency and malaria.

\*  $P < 0.05$  versus controls adjusted for treatment group.

\*\*  $P < .01$  versus controls adjusted for treatment group.

\*\*\*  $P < 0.001$  versus controls adjusted for treatment group.

† Data expressed as geometric mean (95% confidence interval).

‡ Data expressed as arithmetic mean (SD).

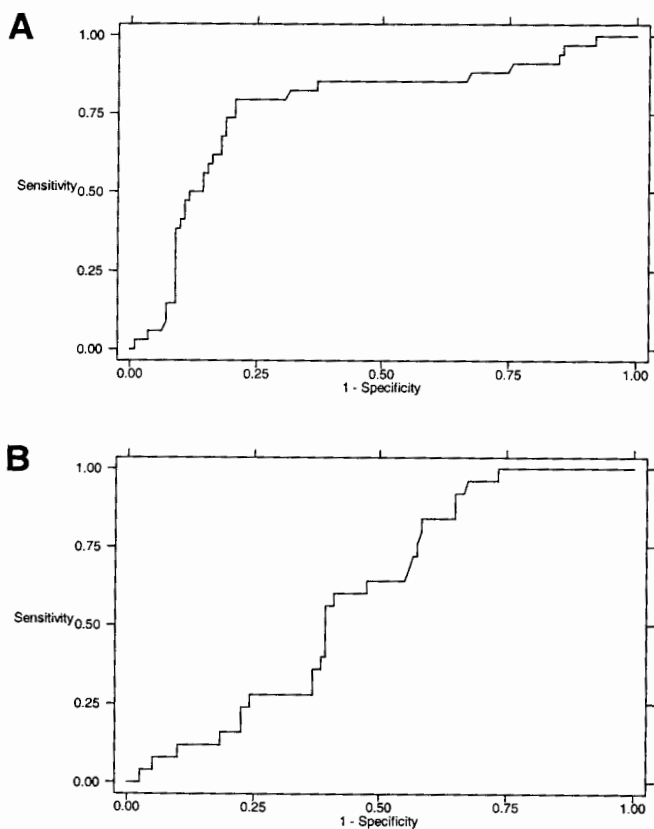


FIGURE 1. The receiving operating characteristics (ROC) curves for sTfR in the identification of children with either malaria-related anemia or IDA. The measurement of sTfR levels gives a sensitivity and specificity greater than 80% in the identification of patients with malaria (A) while sensitivity and specificity could not be obtained simultaneously in the identification of patients with iron deficiency (B).

independently associated with a significant increase in sTfR concentrations. The highest levels of sTfR were in the anemic infants who also had malaria parasitemia. Anemia without malaria infection or iron deficiency was also associated with a smaller but significant increase in sTfR levels (Table 3). Mean sTfR levels were significantly higher in the malaria-anemia group compared to the anemia alone group ( $P < 0.001$ ).

Mean PCV was significantly lower in the malaria-anemia group than in the other two anemic groups ( $P < 0.05$ ), while MCV was lower in IDA and anemia alone groups. Plasma ferritin was significantly higher in the malaria-anemia group. Transferrin concentration was significantly higher in both malaria-anemia and IDA categories. C-reactive protein was significantly increased only in children with both anemia and malaria infection (Table 3).

Figure 1 shows the receiving operating characteristics (ROC) curves for sTfR in the identification of children with either malaria-related anemia or IDA. ROC curves evaluate the sensitivity and specificity of a test taking every value of the sample as a cut-off point to discriminate between two groups. This figure shows that the measurement of sTfR levels gives a sensitivity and specificity greater than 80% in the identification of patients with malaria (A), while sensitivity and specificity could not be obtained simultaneously in the identification of patients with iron deficiency (B).

#### DISCUSSION

This study found that malaria infection was associated with a significant increase in sTfR plasma levels, even above those found in iron deficiency anemia and independent of a concomitant reduction in mean PCV level. This could be solely explained by the hemolysis associated with infection. The direct correlation found between sTfR levels and parasite density supports this. It could be argued that the high sTfR concentration associated with malaria infection could have been a misclassification of some iron deficient children in the absence of a gold standard test for iron deficiency

such as bone marrow examination. However, a significantly ( $P < 0.001$ ) lower MCV in the IDA group compared to the malaria-anemia group is consistent with the assumption that children were correctly classified in this study. It is unlikely that in clinical practice the diagnosis of iron deficiency anemia would be more detailed than it has been in this study.

Plasma sTfR levels are higher in conditions with high erythropoietic activity such as hemolytic conditions (including hemoglobinopathies, congenital hemolytic anemias and traumatic hemolysis), iron deficiency, ineffective erythropoiesis and megaloblastic anemia.<sup>5,15-17</sup> In one study, a significant positive correlation was seen between sTfR and erythropoietin levels in patients with IDA,<sup>5</sup> suggesting that increased erythropoietin production could stimulate the synthesis of sTfR.

Our findings are in disagreement with two other studies carried out among malaria exposed individuals in which plasma sTfR levels were either significantly decreased or not different in the presence of clinical malaria.<sup>8,9</sup> Suppression of the bone marrow response to erythropoietin or its deficiency were proposed to explain the decrease in plasma sTfR levels in individuals with clinical malaria in Vanuatu.<sup>9</sup> However, increased serum erythropoietin levels have been reported in African children with severe malarial anemia<sup>18</sup> and this may be in keeping with the finding of high sTfR levels in association with malaria infection reported in our study. Erythrocyte progenitor cells are considered the main source of transferrin receptors in the body, and the fact that these receptors are increased in malaria may reflect an active erythroid marrow and would argue against the hypothesis that erythropoiesis is inhibited in malaria.<sup>19,20</sup> Reticulocyte counts (which reflect the activity of the erythroid marrow) were found to be decreased in some studies but were normal or increased in others in association with malaria infection, suggesting furthermore that the erythropoietic activity in the bone marrow may be enhanced by malaria infection.<sup>21,22</sup>

Other reasons may explain the discrepancy between the other two studies in malaria endemic areas and ours regarding sTfR levels. First, in the current study, anemic patients were compared with a control group without anemia whereas in the other two studies the groups were not differentiated on the basis of anemia. Different malaria endemicity levels as well as differences in the age of the subjects studied may also contribute to these discrepancies. It is unlikely that the high prevalence of the Hb genotype AS in our study could account for the increased sTfR levels in malaria-infected, anemic children, since sTfR concentration was similar in Hb AA (geometric mean, 95% CI = 4.4 ng/ml, 3.9-4.8) and AS children (geometric mean, 95% CI = 3.8 ng/ml, 3.3-4.5). Furthermore, the proportion of children with the Hb genotype AS was lower among those with malarial-anemia than in the other two anemic and control groups (Menendez C and others, data not shown).

The presence of subpatent malaria parasitemia, or alternatively a malaria infection that has been recently resolved, may explain the moderate but significant increase in sTfR levels in the group with anemia but without malaria or iron deficiency. It is known that the hemolysis of malaria infection may last for days or weeks after the parasitemia has been cleared.<sup>23</sup> Therefore, the hematological effects of ma-

laria may remain, even though parasites are not detected on a blood smear examination.

This study has presented data showing that the measurement of plasma sTfR concentration does not have a role either in individual or population level assessment of iron deficiency in malaria endemic areas, at least in the age group with the highest prevalence of anemia and iron deficiency. Therefore, the accurate detection of iron deficiency anemia in malaria endemic regions by non-invasive methods remains unresolved and more research is needed to find a diagnostic test which helps improving the clinical management of the anemic patients in these areas.

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