*Disorders of Erythropoiesis*

## The usefulness of serum transferrin receptor for discriminating iron deficiency without anemia in children

**We determined serum transferrin receptor (sTfR), serum erythropoietin and hematologic and biochemical iron parameters in 251 healthy children. The levels of sTfR were significantly higher in children with storage iron deficiency but had a poor sensivity for recognizing iron deficiency without anemia. When ferritin values cannot accurately demonstrate the iron deficiency in children, the sTfR/ferritin ratio or sTfR-log ferritin is recommended to discriminate iron deficiency in the absence of anemia.**

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Although the clinical consequences of iron deficiency on growth and development in children are controversial, it can be assumed that iron deficiency poses a serious health problem that pediatricians should be aware of and control.[1] The diagnosis of early iron deficiency states is difficult because iron parameters change according to age, values overlap in various stages of iron deficiency and infections, frequent in children, can alter the sensitivity and specificity of diagnostic algorithms. The levels of serum transferrin receptor (sTfR) are related to the degree of erythropoietic activity and tissue iron deficiency.[2-5] In pediatrics, sTfR has some advantages which make it a potentially useful parameter: it is sensitive,[4] it is specific (since it is not influenced by acute or chronic inflammatory conditions),[3] it shows little biological variability, and its concentration can be determined from a small quantity of serum. However, its value does depend on the method used because of the lack of standarization. The sTfR/ferritin ratio and sTfR-F/log ferritin (sTfR-F index) are widely used parameters in investigations of iron deficiency states, since they have a higher diagnostic power than sTfR or ferritin alone.[4,6] sTfR levels for healthy children have already been published,[7-8] but cut-off values to indicate the beginning of intracellular iron deficiency have not yet been established. The aim of this study was to evaluate the diagnostic usefulness of sTfR and its indices in recognizing iron deficiency without anemia.

A total of 251 healthy children from Almería (159 males), aged 1-10 years, were investigated: 206 (group A) had a normal iron status (data from 155 of them have been previously published)[8] and 45 (group B) had storage iron deficiency (serum ferritin <10 μg/L in children 1-5 years old and <12 μg/L in those 6-10 years old). These children were selected using strict criteria[8] from pediatric surgery outpatient clinics before minor surgical procedures. In all cases, parents gave their informed consent and the study was approved by the hospital Ethics Committee. We measured hemoglobin concentration, red cell indices (including mean corpuscular volume), reticulocyte count, erythrocyte protoporphyrin, transferrin saturation, serum ferritin, serum erythropoietin and sTfR, measured by a enzymoimmunoassay (Quantikine™ IVD™-Human sTfR, RδD Systems Minneapolis, USA). The sTfR/ferritin ratio and sTfR-F index were calculated. We established reference values by age for hematologic and biochemical iron parameters.[1] Group A met all normality criteria. To evaluate the clinical usefulness of sTfR for recognizing iron deficiency states without anemia, receiver operating characteristic (ROC) curves were used, and the maximum diagnostic discrimination cut-off point, (the highest [(sensitivity+specificity)/2] value) was calculated. Table 1 shows a comparison of the hematologic and biochemical parameters between children with normal iron status and those with storage iron deficiency. Figure 1 presents the ROC curves for sTfR, sTfR/ferritin, sTfR-F index, erythrocyte protoporphyrin, transferrin saturation and mean corpuscular volume, and the cut-off points for sTfR and its indices.

**Table 1.** Comparison of mean values of hematologic and biochemical parameters in normal children and in children with storage iron deficiency.

| | *Group A (healthy children with normal iron status)* | *Group B (children with storage iron deficiency)* | *p* |
|---|---|---|---|
| Subjects | 206 | 45 | 0.0001 |
| Hemoglobin (g/L) | 128±9 (126-129) | 123±7 (122-125) | |
| Mean corpuscular volume (fL) | 80±3.6 (79.5-80.7) | 79.2±3.3 (78-80.4) | NS |
| Transferrin saturation (%) | 22.5±7.4 (21.2-23.7) | 21.2±7.5 (19.4-23,1) | NS |
| Erythrocyte protoporphyrin (μmol/L RBC) | 0.41±0.13 (0.39-0.42) | 0.43±0.16 (0.39-0.47) | NS |
| Serum ferritin (μg/L) | 28.6±13.5 (26.4-30.9) | 5.9±-3.4 (5-6.7) | 0,0001 |
| Reticulocyte (×10⁹/L) | 66.5±20.9 (63-70) | 67.4±22,3 (60.9-73.9) | NS |
| Serum erythropoietin (U/L) | 7±4.8 (6.2-7.8) | 8.5±4.6 (7.3-9.6) | NS |
| sTfR (mg/L) | 1.93±0.41 (1.86-1.99) | 2.28±0.5 (2.1-2.4) | 0.0001 |
| sTfR/ferritin ratio | 80±36.8 (73.9-86.2) | 567±358 (478-657) | 0.0001 |
| sTfR-F index | 1.38±0.34 (1.3-1.4) | 4.1±-2.1 (3.6-4.6) | 0.0001 |

*sTfR: serum receptor transferrin; sTfR-F index: serum receptor transferrin/log ferritin. Results are expressed as mean ± standard deviation; the 95% confidence intervals of the mean are given in brackets.*

sTfR was higher in the group of children with storage iron deficiency and this was the only biochemical parameter that showed a significant difference between the two groups of children. These data are consistent with those of Lin *et al.*,[9] who used the RδD Systems method. We found a large overlap of values in between normal and iron deficiency children, although the sTfR level was >2.5 mg/L in 38% of the children with storage iron deficiency, which could suggest the beginning of intracellular iron deficiency. Malope *et al*,[10] observed higher sTfR values as iron deficiency progressed in 561 children aged 1-6 years, but they did not find a significant difference between normal children and those with storage iron deficiency. sTfR/ferritin ratio and sTfR-F index values were much higher in children with storage iron deficiency, and the overlapping disappeared, clearly indicating intracellular iron deficiency.

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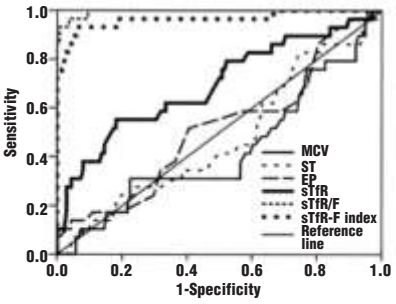


| | AUC (95% CI) |
|---|---|
| MCV | 0,43 (0.34-0.52) |
| TS | 0,47 (0.38-0.56) |
| EP | 0,51 (0.42-0.6) |
| sTFR | 0,69 (0.61-0.78) |
| sTFR/F Ratio | 0,995 (0.989-1) |
| sTFR-F Index | 0,96 (0.93-0.997) |

| Cut-off point | Se (95% CI) | Sp (95% CI) | PPV (95% CI) | NPV (95% CI) |
|---|---|---|---|---|
| sTfR>2.5 | **38**(28-51) | **92**(86-96) | **67**(48-81) | **75**(68-81) |
| sTfR/F>175 | **94**(84-98) | **97**(92-99) | **94**(84-98) | **97**(92-99) |
| sTfR-F Index >2 | **89**(78-94) | **96**(90-98) | **90**(79-96) | **94**(89-97) |

*MCV, mean corpuscular volume; TS, transferrin saturation; EP, erythrocyte protoporphyrin; AUC, area under curve; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value. The cut-off points were calculated to be those with the highest (sensitivity+specificity)/2 valve. The cut-off point for the sTfR indices were identical to P95 values for normal children (Group A). In situations of erythropoietic normality, with the methodology employed, values higher than the calculated cut-off point could suggest the beginning of intracellular iron deficiency.*

**Figure 1.** Receiver operating characteristic curves for sTfR, its indices and other iron parameters in detecting iron deficiency without anemia, and the cut-off points for sTfR, the sTfR/ferritin ratio and the sTfR-F index.

The difference in hemoglobin concentrations observed between the two groups was considered clinically not relevant, and differences were not found in serum erythropoietin and reticulocyte counts, probably indicating that iron deficiency, and not high erythropoietic activity, was responsible for the increase of sTfR in the group with iron deficiency. The interest in measuring sTfR levels in children lies in the usefulness of this parameter to diagnose early iron deficiency states. In iron deficient adults, sTfR has been shown to have a better sensitivity and specificity than classical diagnostic tests, and cut-off values for functional iron-deficiency have been stablished.[4,6] Using ROC curves we observed that the sensitivity of sTfR for discriminating children with storage iron deficiency was poor, but it was better than that of the other parameters related to the functional iron compartment (Figure 1). Erythrocyte protoporphyrin and mean corpuscular volume are parameters that alter late in iron deficiency and transferrin saturation is affected by variations in the level of serum iron and total iron binding capacity. The cut-offs with greatest diagnostic accuracy were 2.5 mg/L for sTfR (with low sensitivity but high specificity), 175 for the sTfR/ferritin ratio and 2 for the sTfR-F index, with a high sensitivity and specificity. We have not found any studies to compare our results.

Overall, we conclude that decreased ferritin is the basic marker for detecting iron deficiency in children. However, in children whose ferritin concentration is in a range in which no decision can be made, calculation of the sTfR/ferritin ratio or sTfR-F index is recommended in order to discriminate iron deficiency in the absence of anemia. The cut-off value of the sTfR assay for adults cannot be recommended in children because of its low diagnostic sensitivity in iron deficiency without anemia. There is an urgent need to standardize the method and to carry out large epidemiological studies to obtain international reference values.

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