



The role of serum transferrin receptor in the diagnosis of iron deficiency

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Abstract

Background and Objective. Iron deficiency anemia (IDA) is often associated with inflammatory disorders. The most conventional parameters of iron metabolism are therefore affected, making the evaluation of iron status difficult. Serum transferrin receptor (sTfR) levels are raised in iron deficiency but are not influenced by inflammatory changes. The aim of this study was to investigate the role of sTfR in differentiating IDA with inflammatory features.

Design and Methods. A diagnostic study of sTfR measured by immunoassay was carried out in IDA and anemia of chronic disorders (ACD). The cut-off points of sTfR and the ratio of sTfR/serum ferritin, which were obtained after comparing IDA and ACD, were applied to a group of 64 patients with mixed iron patterns (MIX) (16 with ACD and 48 with IDA).

Results. The best cut-off point of sTfR between IDA and ACD was 4.7 mg/L. Applying this cut-off to the MIX group, an efficiency of 87% was obtained (sensitivity 92% and specificity 81%). This level of sTfR correctly classified 53 out of 64 cases of the MIX group (83%). Using the ratio of sTfRx 100/serum ferritin, the best cut-off point was 8 (efficiency 100%), which correctly classified 62 out of 64 cases of the MIX group (97%).

Interpretation and Conclusions. This study demonstrates that sTfR in conjunction with other iron parameters is very useful in iron deficiency evaluation, especially in hospital practice. Iron treatment should be considered in patients with mixed patterns of iron status, in which the diagnosis of IDA versus ACD is difficult, when the levels of sTfR exceed the cut-off point.

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Key words: serum transferrin receptor, serum ferritin, iron deficiency

Ferritin and transferrin receptor are proteins that participate in iron homeostasis. The production of these proteins is finely regulated and co-ordinated at transcriptional levels by iron bioavailability.¹ Serum ferritin, which generally reflects the size of iron stores, is regarded as a mark-

er in the evaluation of iron status in the absence of inflammation. In inflammatory disorders, however, a cytokine-mediated pathway can activate the ferritin gene, causing the hyperferritinemia which commonly occurs in these disorders. This mechanism is iron independent.²

Transferrin receptor (TfR) is a transmembrane protein. Practically all cells possess TfR on their surfaces despite the fact that most TfRs are on erythroid cells. Soluble (serum) TfR (sTfR) is a truncated form of the cellular receptor.³ Several studies have demonstrated an increase in sTfR in iron deficiency anemia and a lack of influence of inflammatory changes.⁴⁻⁶

In general practice, especially in hospitals, iron deficiency is often associated with inflammatory features, with the result that the typical iron pattern of iron deficiency anemia is mixed with the iron pattern of anemia of chronic disorders.⁷ The most conventional parameters of iron metabolism are, therefore, affected, hindering the evaluation of iron status.

In this work, sTfR was studied in a group of patients with typical iron deficiency anemia and in another with anemia of chronic disorders. The diagnostic value of sTfR was subsequently evaluated in a group of anemias with mixed iron patterns.

Materials and Methods

Blood cell counts, sedimentation rate, reticulocytes and their maturity fractions, haptoglobin, bilirubin, serum iron, total iron binding capacity, saturation index, and serum ferritin were measured in all cases and the patients' clinical data were recorded.

Serum TfR was measured by a commercial immunoassay (QUANTIKINE™, Transferrin receptor ELISA kit, R&D Systems, Minneapolis, USA) in a group of 32 patients with typical iron deficiency anemia (serum iron, Fe \leq 9 μ mol/L, total iron binding capacity \geq 70 μ mol/L and serum ferritin \leq 13 μ g/L). A group of patients with anemia of chronic disorders was also evaluated (Fe: \leq 9 μ mol/L, total iron binding capacity $<$ 40 μ mol/L, and serum ferritin \geq 100 μ g/L) (Table 1). The results from both groups were compared and the diagnostic value of sTfR was investigated using the receiver-operator (ROC) curve (Graph ROC for Windows version 2.0, Turku, Finland) and logistic regression methodologies. Subsequently, the cut-off points for sTfR and for sTfR \times 100/serum ferritin ratio^{8,9} were calculated.

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Table 1. Values obtained in the population studied.

	Hb g/L	MCV fL	SR mm Hg/h	sFt µg/L	sTfR mg/L	sTfRx100/sFt
IDA (n=32)	93±3 (46-120)	74±2 (50-90)	17±9 (6-38)	6±1 (1-12)	11±1 (3.9-34)	539±814 (32-3400)
ACD (n=39)	89±2 (54-114)	89±1 (78-98)	102±27 (41-140)	384±40 (121-1100)	3.4±0.2 (1.2-5.7)	1.3±0.8 (0.1-3)
Mixed (n=64)	92±2 (35-119)	82±1 (56-100)		74±15 (1-778)	7±5.1 (1.2-24)	
Reference (n=65)					2.6±0.1 (1.7-3.7)	

IDA, iron deficiency anemia. ACD, anemia of chronic disorders. sFt, serum ferritin. sTfR, serum transferrin receptor. SR, sedimentation rate. Results are expressed as mean ± standard deviation. In brackets, maximum and minimum values.

The cut-off points were applied to a group of anemias in which iron variables showed mixed patterns (mixed group). After clinical evaluation, these 64 patients were divided into two groups (Tables 1 and 2). In 16 cases of the mixed group, an anemia of chronic disorders was detected by iron staining in bone marrow. In the remaining 48 cases, iron deficiency anemia was confirmed by response to iron treatment.

Of the 48 cases of the mixed group with iron deficiency anemia, 8 patients had serum ferritin ≤ 13 µg/L, but Fe or total iron binding capacity was not typical of iron deficiency anemia; 12 had serum ferritin ≥ 13 µg/L, but Fe and total iron binding capacity were typical of iron deficiency anemia; and, finally, 28 cases had an iron deficiency anemia without these patterns.

Results

As expected, there was a significant difference in sTfR between iron deficiency anemia and anemia of chronic disorders [sTfR in iron deficiency anemia was 10.9 mg/L and in anemia of chronic disorders 3.4 mg/L (difference 7.54 mg/L; 95% confidence interval: 4.6-10.5 mg/L; $t = 5.2$, $p < 0.0001$) (Table 1)].

There was no significant difference in Hb between iron deficiency anemia and anemia of chronic disorders ($t = 1.08$, $p = 0.29$), but there was a negative relationship between Hb and sTfR in iron deficiency anemia ($\log \text{TfR} = -0.012\text{Hb} + 2.09$, $r = -0.85$). This relationship was not demonstrated in anemia of chronic disorders.

Using the logistic regression, the equation to classify iron deficiency anemia ($y = 1$) versus anemia of chronic disorders ($y = 0$) was $y = 1 / 1 + e^{-(-9.61 + sTfR \cdot 2.003)}$. The best cut-off point of sTfR was 4.7 mg/L (efficiency 0.87; sensitivity 0.92; specificity 0.81). In the case of sTfR × 100/serum ferritin ratio, the cut-off point was 8 (efficiency 100%).

Applying these cut-off points to the mixed group,

sTfR correctly classified 53 out of 64 cases and the ratio of sTfR/serum ferritin classified 62 cases (exceptions: one case with anemia of chronic disorders, a Hb of 105 g/L and a ratio of 11 and one case with iron deficiency anemia, a Hb of 106 g/L and a ratio of 6).

When studying the sTfR data in the mixed group, it was observed that the sTfR was lower than 4.7 mg/L in 14 out of 16 cases with anemia of chronic disorders (exceptions: one case had a Hb of 109 g/L

Table 2. Characteristics of the cases included in the mixed group.

	Iron deficiency	Anemia of chronic disorders
Cases	48	16
Clinical data	Cardiopathy 17 Neoplasia 7 Infection 4 Arthritis 8 Endocrinopathy 5 Others 7	Lymphoma 7 Solid tumors 2 Monoclonal gammopathy 1 Cytopenias 6 (5 collagen disorders, 1 tuberculosis)
Hb g/L	89±18 (pre-treatment) (35-115) 125 (post-treatment) (110-151)	97±15 (59-119)
SR mm Hg/h	41±27 (3-115)	77±30 (6-140)
sFt µg/L	30±17 (1-80)	208±195 (31-778)
sTfR mg/L	8.1±5.4 (3.7-24)	3.5±1.2 (1.2-6.6)
sTfRx100/sFt	85±288 (6-2000)	3±3 (0.4-11)

sFt, serum ferritin. sTfR, serum transferrin receptor. SR, sedimentation rate. Results are expressed as mean ± standard deviation. In brackets, maximum and minimum values.

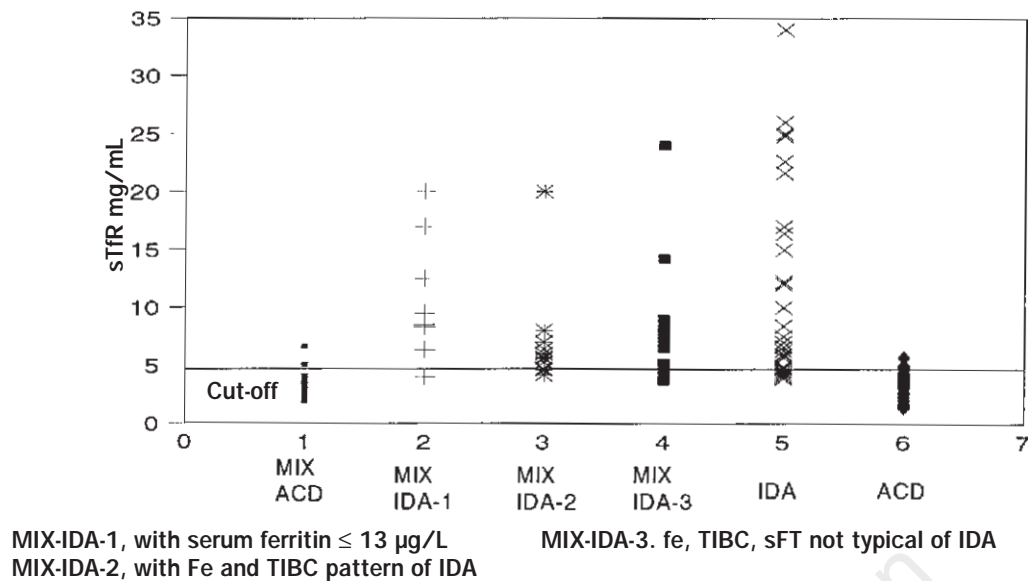


Figure 1. Serum transferrin receptor in iron deficiency anemia (IDA), anemia of chronic disorders (ACD) and the mixed group (MIX).

and sTfR of 5.1 mg/L and another a Hb of 59 g/L and 6.6 mg/L of sTfR).

In the case of iron deficiency anemia of the mixed group, in patients with serum ferritin $\leq 13 \mu\text{g/L}$, 7 out of 8 cases had a sTfR that exceeded 4.7 mg/L (exception: Hb 115 g/L and sTfR 4.0 mg/L). In the group with low Fe and raised levels of total iron binding capacity, but with serum ferritin higher than 13 $\mu\text{g/L}$, 10 out of 12 patients revealed a sTfR exceeding the cut-off level (exceptions: Hb 99 g/L and 4.6 mg/L of sTfR; Hb 94 g/L and 4.2 mg/L of sTfR). In the remaining 28 cases, 20 patients had sTfR values exceeding the cut-off level (in the exceptions, Hb ranged from 63 to 109 g/L and sTfR from 3.7 to 4.6 mg/L) (Figure 1).

Discussion

In clinical practice, iron deficiency associated with inflammatory disorders is frequent, with the result that the presence of mixed patterns of iron variables is not unusual. This is especially important in hospital practice where inflammatory disorders are very common. The differentiation between anemia of chronic disorders and iron deficiency with inflammatory traits is a daily problem. A number of methods have been devised to rule out iron deficiency in chronic inflammatory disorders.

In this regard, some authors have demonstrated that levels of serum ferritin > 30 ,⁵ > 60 ¹⁰ or $> 90 \mu\text{g/L}$,¹¹ higher than those observed in iron deficiency anemia (< 13 or $< 20 \mu\text{g/L}$), are more efficient cut-off points in the presence of inflammation. A second method of

detecting the presence of iron deficiency is the response to iron treatment.¹¹ Finally, the method that is regarded as the gold standard is the evaluation of iron in the bone marrow. However, this evaluation is a method that is subjective and aggressive, despite being, in some cases, the only technique for diagnosing iron deficiency.^{12,13}

Serum transferrin receptor is a good candidate for assessing bone marrow erythropoiesis in several diseases^{6,14,15} and therefore for predicting a possible response to treatment with erythropoietin¹⁶ or hematitics.^{17,18}

Serum TfR is higher in iron deficiency anemia than in anemia of chronic disorders.^{4-6,8} However, few studies have been carried out to investigate the role of sTfR in the differential diagnosis of anemias with mixed patterns of iron variables, especially contrasting serum ferritin and sTfR. On the other hand, some authors have questioned the usefulness of sTfR as the only test for detecting iron deficiency.¹⁹

Bearing this in mind, this study lends support to the view that sTfR is very useful in iron deficiency evaluation in hospital practice, confirming the view that the sTfR and the ratio of sTfR/serum ferritin are good parameters for predicting the presence of iron deficiency concomitant with inflammatory diseases.^{8,9} Subsequently, when the sTfR values were applied to a group of mixed anemias, they showed a high efficiency and in the case of the sTfR/serum ferritin ratio, the diagnostic efficiency was almost 100%.⁸

These results suggest that levels of sTfR in conjunction with the classic iron parameters (Fe, total

iron binding capacity and saturation index) are at least as useful as the levels of serum ferritin plus classic iron variables in studying iron deficiency. This could be especially true in hospital medicine, where mixed patterns of iron parameters are the rule and where serum ferritin, an acute phase reactant, is often raised owing to a cytokine-mediated inflammatory mechanism.

The levels of serum TfR evaluated together with other iron parameters are very useful in the diagnosis of patients with anemia, in whom the differential diagnosis between iron deficiency and anemia of chronic disorders is difficult. Our results agree with the findings of other groups,^{8,9} but are in contrast with others,¹⁹ probably because, in this field, sTfR should be evaluated in conjunction with other iron parameters, and not as a parameter alone.

In summary, sTfR detects iron deficiency in the case of mixed patterns of iron variables. Given that sTfR is very helpful in iron status management, generalization of its investigation is warranted. Iron treatment should be recommended when sTfR exceeds the cut-off point.

Contributions and Acknowledgments

AFR participated in the conception and design of the study, carried out the analysis of results and wrote the paper. MPS, MP and JU carried out the biochemical measurements. RM was involved in the clinical assessment of patients.

Disclosures

Conflict of interest: none.

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