

Soluble transferrin receptor as a diagnostic laboratory test for detection of iron deficiency anemia in acute illness of hospitalized patients

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ABSTRACT: **Background:** Many patients in the internal medicine ward have anemia. The etiology for the anemia may be multifactorial and, in the setting of inflammatory process when the ferritin is increased, it is difficult to diagnose iron deficiency anemia. Soluble transferrin receptor (sTfR) had been suggested as an indicator for iron deficiency. No study has investigated the meaning of high sTfR as the only positive marker of iron deficiency anemia (IDA) caused by gastrointestinal tract (GIT) bleeding in hospitalized patients. **Objectives:** To demonstrate the importance of high levels of sTfR as a marker for further GIT investigation in cases of anemia where the level of ferritin was normal or increased. **Methods:** We retrospectively assessed all patients in an internal medicine ward in our facility who had anemia, high sTfR levels (> 5.0 mg/L) and normal or high ferritin levels and who underwent esophagogastroduodenoscopy and colonoscopy. **Results:** Of 32 patients with anemia and normal or high ferritin levels and high sTfR, 22 patients (68%) had findings that explained IDA (in some patients more than one finding). Those findings were colonic polyps (n=9), carcinoma of colon (n=4), duodenal ulcer (n=4), carcinoma of stomach (n=3), colitis (n=3), atrophic gastritis (n=1), erosive gastritis (n=1) and angiodysplasia (n=1). **Conclusions:** High sTfR may be a good indicator of IDA caused by GIT bleeding when the ferritin level is normal or high. GIT investigation is warranted in such cases.

IMAJ 2011; 13: 96–98

KEY WORDS: soluble transferrin receptor, iron deficiency anemia, gastrointestinal bleeding, ferritin

Iron deficiency is the most common form of anemia encountered in clinical practice and it is commonly a manifestation of chronic occult gastrointestinal tract bleeding. Current evidence suggests that a substantial number of men and postmenopausal women with iron deficiency

sTfR = soluble transferrin receptor
IDA = iron deficiency anemia
GIT = gastrointestinal tract

anemia harbor significant GIT lesions that are the source of blood loss [1]. As such, the evaluation of patients with IDA is generally focused on the GIT. Importantly, the diagnosis of IDA should be firmly established before an extensive evaluation is undertaken.

Serum iron and serum ferritin are laboratory tests commonly used for the detection of iron deficiency; however, their values may be falsely changed in complex medical situations [2]. Plasma iron transport is carried out by transferrin, which delivers iron into cells through its interaction with a specific membrane receptor, the transferrin receptor [3]. When iron deficiency exists, the soluble transferrin receptor concentration in serum rises even before the hemoglobin concentration is significantly depressed. The sTfR concentration can therefore describe the functional iron status, while ferritin reflects the iron storage status [4,5].

Studies have shown that the level of sTfR is markedly elevated in IDA but remains normal in anemia due to chronic inflammation without iron deficiency and thus may be of considerable help in differentiating between IDA and anemia of chronic disease [6-8]. In addition, use of the formula sTfR/log ferritin ratio may increase the efficacy of sTfR in identifying iron deficiency in patients with chronic inflammation. A ratio of less than 1 suggests anemia of chronic disease, whereas a ratio of more than 2 suggests absolute iron deficiency coexisting with anemia of chronic disease [9,10].

Iron deficiency anemia may be especially marked in hospitalized patients in whom, for many reasons, acute-phase reactants may be high. So far, no study has investigated the correlation between high sTfR levels and positive GIT findings in hospitalized patients when levels were normal or high. The aim of our study was to show the importance of high levels of sTfR as a marker for further GIT investigation in cases of anemia where the level of ferritin was normal or increased.

PATIENTS AND METHODS

In this study we reviewed the records of patients with anemia who were hospitalized in the Department of Medicine E at

the Meir Medical Center between August 2003 and February 2005. We included all patients whose soluble transferrin receptor was high (> 5.0 mg/L). Anemia was defined as a hemoglobin level < 13 g/dl in men or < 12 g/dl in women.

Laboratory studies included complete blood count, ferritin (serum ferritin level < 30 ng/dl), iron (serum iron level < 50 µg/dl) and serum transferrin (> 360 mg/dl). To measure sTfR levels, we used the Tina-quant sTfR on the Roche/Hitachi 917 and nephelometric sTfR methods.

Patients with anemia and a low ferritin level were excluded from the study. Patients with anemia, high sTfR, and normal or high ferritin levels underwent esophagogastroduodenoscopy and colonoscopy. The endoscopies were performed using standard video endoscopes. Duodenal and gastric biopsies were taken during the procedures.

The following GIT abnormalities were considered a possible etiology of IDA: erosive esophagitis, erosive gastritis, atrophic gastritis, gastric and duodenal ulcers, gastric tumors, erosive duodenitis, celiac disease, inflammatory bowel disease, diverticulosis, colorectal tumors, angiodysplasia, and colonic polyps larger than 1 cm.

RESULTS

Thirty-two patients (20 men and 12 women, mean ± SD age 68.84 ± 13.09 years) met the inclusion criteria of anemia, high sTfR level and normal or high ferritin level. The mean hemoglobin level was 10.28 g/dl (range 5.6–11.5 g/dl), the mean sTfR level was 7.62 mg/L (range 5.0–17.8 mg/L), and the mean sTfR/log ferritin ratio was 3.89 (range 2.02–8.7); in two patients it was less than 2.0.

Patients in whom anemia was detected were hospitalized mainly because of infections, congestive heart failure, exacerbation, weakness, chest pain, and autoimmune diseases. The cause of admission was gastrointestinal tract-related in only five patients [Table 1].

Table 1. Cause of hospitalization

Reason for hospitalization	No. of patients
Infections	8
Congestive heart failure	6
Chest pain	2
Weakness	3
Autoimmune diseases	5
Weight loss	2
Abdominal pain	2
GIT bleeding	1
Other	3
Total	32

Table 2. Etiology of anemia in the study group of 32 patients

	Detected by endoscopy
Malignant causes	
Carcinoma of stomach	3
Carcinoma of colon	4
Benign causes	
Atrophic gastritis	1
Erosive gastritis	1
Duodenal ulcer	4
Ulcerative colitis, other colitis with erosions	3
Colonic polyps	9
Angiodysplasia	1
Total	26*

*Eight patients refused endoscopy

Patients underwent GIT investigation by esophagogastroduodenoscopy and/or colonoscopy. Of these, 24 underwent esophagogastroduodenoscopy and colonoscopy at the same time, 4 underwent only colonoscopy and 4 underwent esophagogastroduodenoscopy. Esophagogastrosocopy and colonoscopy detected the cause of IDA in 22 patients (68%). Six patients (32%) had lesions in the upper GIT that explained the origin of the IDA, 11 (50%) had lesions in the lower GIT, and 5 (23%) had lesions in both the upper and lower tract [Table 2].

GIT investigation was not completed in eight patients, who refused to undergo either esophagogastrosocopy or colonoscopy.

DISCUSSION

Iron transport in the plasma is carried out by transferrin, which delivers iron into the cells through its interaction with a specific membrane receptor. This receptor – the transferrin receptor – is a 760-amino acid glycoprotein.

Receptor density on proliferating cells is inversely related to the availability of iron, as iron deprivation results in prompt induction of TfR synthesis, whereas excess iron suppresses TfR numbers. Therefore, the total amount of TfR depends both on the number of erythroid precursors in the bone marrow and on the number of TfR per cell, a function of the iron status of the cell [3]. Since 80–95% of the transferrin receptor molecules are localized on erythropoietic cells, the TfR concentration (and hence also the sTfR concentration) reflects the iron requirement of these cells. When iron deficiency exists, the sTfR concentration in serum rises even before the hemoglobin concentration is significantly depressed. The sTfR concentration can therefore describe the functional iron status, while ferritin reflects the iron storage status [4,5]. Increased sTfR levels are seen in situations of

TfR = transferrin receptor

stimulated erythropoiesis, such as hemolytic anemia [11], thalassemia major or intermedia [12], sickle cell disease [13], magaloblastic anemia, or secondary polycythemia [14]. Patients with inflammation of unknown origin, anemia of chronic disorders [7], human immunodeficiency virus infection [15], acute infection [7] or chronic liver disorders [7] do not have increased sTfR levels. On the other hand, patients with anemia due to chronic disorders may also have concomitant true iron deficiency and therefore have sTfR levels elevated to similar levels as in pure IDA, even if these studies were not always based on a gold standard such as marrow iron determination [8,16-19]. In contrast to serum ferritin, sTfR may thus be a useful diagnostic tool for detecting iron deficiency in patients with inflammation.

Several studies have demonstrated the importance of sTfR in inflammatory conditions. Baillie et al. [20] checked the importance of sTfR concentrations against the gold standard of iron stores, bone marrow iron. The sTfR concentration was shown to be the most efficient test in predicting bone marrow iron stores in 20 patients with anemia of chronic diseases (75% efficiency) and in 18 patients with rheumatoid arthritis (94% efficiency). Lee and co-workers [21] evaluated the diagnostic performance of sTfR, ferritin, and sTfR index as a marker for IDA compared to the gold standard of bone marrow iron store in 120 patients with anemia due to several groups of diseases (IDA, chronic inflammation or infection, and non-hematologic malignancy). Their conclusion was that sTfR was not superior to ferritin for detecting iron depletion. They also concluded that in patients with a non-hematologic malignancy, sTfR did not reflect the iron status because of its unknown mechanism. Another conclusion of that study was that patients with chronic diseases require different serum ferritin cutoff levels based on diagnostic classification [21].

Using the ratio of sTfR/log ferritin may increase the efficacy of sTfR in identifying iron deficiency in patients with chronic inflammation. A ratio of less than 1 suggests anemia of chronic disease, whereas a ratio of more than 2 suggests absolute iron deficiency coexisting with anemia of chronic disease [9,10].

The above studies suggest that sTfR may be an indicator for iron deficiency anemia. Yet, no research so far has investigated the etiology of IDA in those patients. In the present study we found that sTfR is a strong indicator for IDA, even when the ferritin level was normal or high, and that in 68% of the patients a gastrointestinal etiology for their anemia was found. Furthermore, in one-third of those patients a GIT malignancy was detected. In all those patients the sTfR was the sole indicator for the malignancy.

In this study we used sTfR as a detection marker for IDA in patients with normal or high levels of ferritin. We recommend checking sTfR levels and using the results as a guideline for further GIT investigation in cases of anemia with normal or high ferritin levels.

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