Usefulness of the serum ferritin concentration in the detection of iron deficiency in a general hospital

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The efficacy of measuring the transferrin saturation and the serum ferritin concentration to detect iron deficiency was determined under routine conditions in a general hospital. The tests were performed on 100 adult patients who consecutively underwent bone marrow aspiration for the appraisal of a wide range of clinical conditions. The absence of stainable reticuloendothelial iron in smears of the aspirate was used as the benchmark of iron deficiency.

Of the 86 patients who were anemic 19 lacked hemosiderin in the bone marrow. The percentage of patients with iron deficiency who were correctly classified by the tests (i.e., the tests' sensitivity) was 84% for the transferrin saturation and 79% for the serum ferritin concentration, and the percentage of patients free of iron deficiency who were correctly classified by the tests (i.e., the tests' specificity) was 63% and 96% respectively. The predictive value of an abnormal (positive) result for the detection of iron deficiency was 39% for the transferrin saturation and 83% for the serum ferritin concentration, whereas the predictive value of a normal or high (negative) result for the exclusion of iron deficiency was 93% and 94% respectively. Measurement of the serum ferritin concentration was superior to measurement of the transferrin saturation only in its specificity. The former is of particular value in clinical settings where the prevalence of iron deficiency is low and conditions that increase the serum ferritin concentration out of proportion to the size of the body iron stores are infrequent.

L'efficacité de la mesure de la saturation à la transferrine et de la concentration sérique de ferritine pour détecter une carence en fer a été déterminée dans les conditions de pratique courante d'un hôpital général. Les tests ont été effectués chez 100 patients adultes consécutifs qui ont subi une aspiration de moëlle osseuse pour l'évaluation d'une grande diversité d'affections. L'absence de fer réticuloendothélial colorable dans le frottis des prélèvements d'aspiration a été utilisée comme point de repère d'une carence en fer.

Sur les 86 patients anémiques, 19 manquaient d'hémosidérine dans la moëlle osseuse. Le pourcentage des patients souffrant d'une carence en fer qui ont été classifiés correctement par les tests (i.e., la sensibilité des tests) a été de 84% pour la saturation à la transferrine et de 79% pour la concentration sérique de ferritine, et le pourcentage des patients exempts de carence en fer qui ont été classifiés correctement par ces tests (i.e., la spécificité des tests) a été de 63% et de 96% respectivement. La valeur prévisionnelle d'un résultat anormal (positif) a été de 39% pour la saturation à la transferrine et de 83% pour la concentration sérique de ferritine, alors que la valeur prévisionnelle d'un résultat normal ou élevé (négatif) pour l'exclusion d'une carence en fer a été de 93% et de 94% respectivement. La mesure de la concentration sérique de ferritine s'est avéré supérieure à la mesure de la saturation à la transferrine uniquement pour ce qui est de sa spécificité. La première épreuve est particulièrement utile dans les milieux cliniques où la fréquence des carences en fer est faible et où les maladies capables d'augmenter la concentration sérique de ferritine de façon disproportionnée par rapport à l'importance des réserves corporelles de fer sont peu fréquentes.

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Determination of the serum ferritin concentration is now well established for the assessment of body iron stores in healthy individuals[1,2] and it has been successfully applied to nutritional surveys of people in Canada[3] and the United States.[4] The serum ferritin concentration is reduced in iron deficiency anemia and is increased in iron loading disorders, but the clinical application of its measurement has been limited by the finding that common conditions such as cirrhosis, chronic inflammation and hematologic malignant conditions increase its concentration out of proportion to the size of body iron stores.[1,2] The practical implications of these nonspecific effects on the efficacy of measuring the serum ferritin concentration to detect iron deficiency have not been fully investigated.

The purpose of the study described in this paper was to determine, under routine conditions in a general hospital, the sensitivity, specificity and predictive value of measuring the serum ferritin concentration to detect iron deficiency in patients with anemia. The absence of hemosiderin from smears of a bone marrow aspirate was used as the benchmark of iron deficiency.

Methods

Selection of subjects

The subjects were adult patients at University Hospital, London, who required bone marrow aspiration for appraisal of their condition. This report is based on the results obtained for 100 patients who consecutively underwent bone marrow aspiration during a 4-month period. A blood sample was obtained within 48 hours of aspiration for measurement of hemoglobin concentration, serum iron concentration, percent transferrin saturation and serum ferritin concentration. The diagnoses of the patients' conditions were obtained from a review of the hospital charts.

Hemoglobin

The hemoglobin concentration was measured with a Coulter counter (model 'S'). Normal values are 11.5 to 14.0 g/dL for women and 13.5 to 18.0 g/dL for men.

Serum iron and transferrin saturation

The serum iron concentration and the transferrin saturation were measured with a diagnostic kit obtained from Hoffmann–La Roche Limited, Vaudreuil, PQ. The normal ranges given were 65 to 175 μg/dL for the former and 20% to 55% for the latter. For this study a serum iron concentration of less than 65 μg/dL and a transferrin saturation of less than 20% were considered abnormal.

Serum ferritin

A radioimmunoassay with labelled

ferritin was used for measurement of the serum ferritin concentration.[5] The protein concentration assigned to the ferritin standards was determined by the Lowry method.[6] In accord with the recommendations of Luxton and coworkers[5] the lower limit of normal for both men and women was taken as 18 ng/mL.

Bone marrow hemosiderin

Smears of bone marrow aspirates stained with Prussian blue were evaluated by one of us (R.M.B.). The reports issued to the attending physicians were reviewed, and the grade of bone marrow hemosiderin given in the report was used for this study.

Analysis of data

To evaluate the usefulness of measuring the serum ferritin concentration to predict the presence or absence of body iron stores, we calculated the sensitivity, specificity, efficiency and predictive value of this test in comparison with the others used as follows, expressing the fractions as percentages:[7]

Sensitivity = TP/(TP + FN)
Specificity = TN/(TN + FP)
Efficiency = TP + TN/(TP + FP + FN + TN)
Predictive value of a positive result = TP/(TP + FP)
Predictive value of a negative result = TN/(TN + FN)

where TP = true-positive, FN = false-negative, TN = true-negative and FP = false-positive.

Results

Anemia

The 14 patients who had a normal hemoglobin concentration were not studied further. Of the remaining patients 19 lacked hemosiderin in the reticuloendothelial cells of the bone marrow.

Serum iron

The serum iron concentration was less than 65 μg/dL in 16 of the 19 patients lacking marrow hemosiderin, and was greater than this value in 29 of the 67 patients with stainable iron in the marrow.

Transferrin saturation

The percent transferrin saturation was less than 20% in 16 of the 19 patients lacking bone marrow hemosiderin and in 25 of the 67 patients with stainable iron in the bone marrow.

Serum ferritin

The serum ferritin concentration was less than 18 ng/mL in 15 of the 19 patients lacking bone marrow hemosiderin (Fig. 1). Of the 15, 11 had uncomplicated iron deficiency, 3 had chronic inflammation and 1 had a solid tumour. Of the four patients with a normal serum ferritin concentration two had a hematologic malignant disorder, one had rheumatoid arthritis and one had idiopathic thrombocytopenic purpura.

The serum ferritin concentration was less than 18 ng/mL in only 3 of the 67 patients with reticuloendothelial hemosiderin.

Sensitivity and specificity of tests

The tests had equivalent sensitivity whether used alone or in combination (Table I). The specificity of measuring the serum ferritin concentration was greater than the specificity of measuring the serum iron concentration or the transferrin saturation. Combining measurement of the serum ferritin concentration with that of the serum iron concentration or the percent transferrin saturation had no significant effect on sensitivity but it reduced the specificity of the serum ferritin test.

Predictive value of test results

The predictive values of normal percentages of transferrin saturation and normal serum ferritin concentrations for excluding iron deficiency were 93% and 94% respectively (Table II). The predictive value of a low percent transferrin saturation was only 39%, compared with a value of 83% for a low serum ferritin concentration.

Discussion

Making a diagnosis of severe iron deficiency anemia is not difficult. A history of blood loss, hypochromic anemia, diminished transferrin saturation and absence of bone marrow hemosiderin are characteristic features.[8] Mild iron deficiency is more difficult to detect. Hypochromic and microcytic erythrocytes are not always present, and the percent transferrin saturation may be within normal limits. Iron deficiency associated with chronic inflammation or malig-

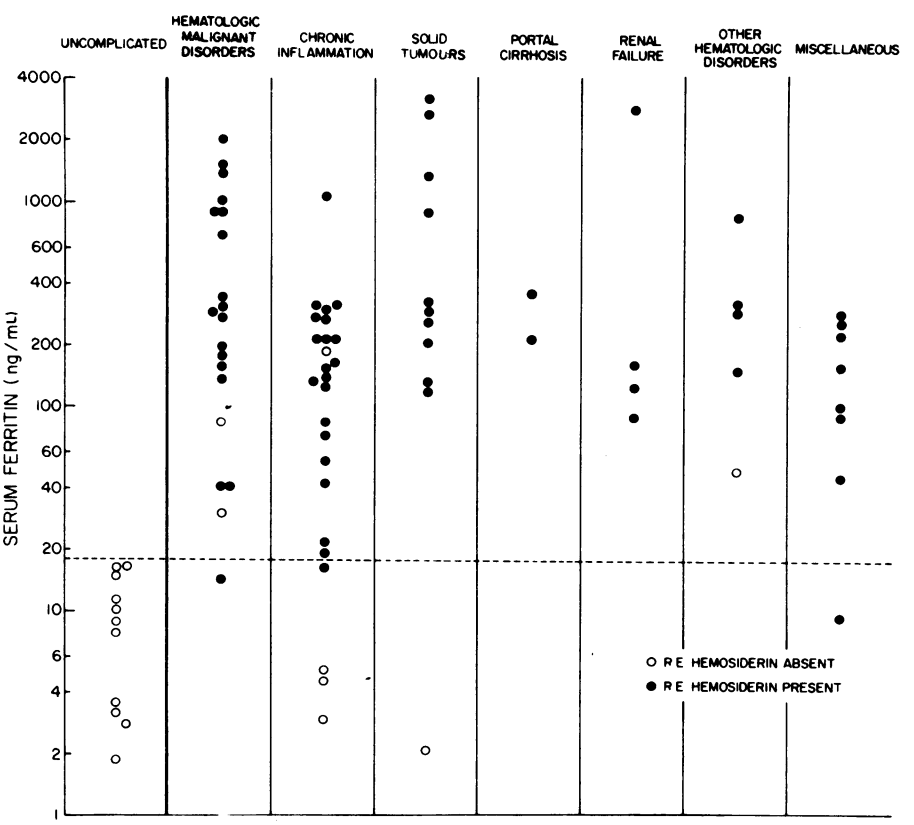

FIG. 1—Serum ferritin concentration in patients with anemia associated or not with various disease processes. Broken line indicates lower limit of normal range of values. RE = reticuloendothelial.

Table I—Sensitivity, specificity and efficiency of measuring transferrin saturation and serum ferritin concentration to detect iron deficiency in anemic patients (expressed in percentages)

Variable measured	Sensitivity*	Specificity†	Efficiency‡
Serum iron concentration	84	43	52
Transferrin saturation	84	63	67
Serum ferritin concentration	79	96	92
Serum iron and serum ferritin concentrations together	84§	42	51
Transferrin saturation and serum ferritin concentration together	84§	50	64

*Percentage of patients lacking bone marrow hemosiderin and having a positive (low) test result.
†Percentage of patients having bone marrow hemosiderin and a negative (normal or high) test result.
‡Percentage of patients with a correct-negative or correct-positive test result.
§Percentage of patients with positive (low) results for either test or for both tests.

Table II—Predictive value of transferrin saturation and serum ferritin concentration in anemic patients

Variable measured	Predictive value of	
	Positive test result*	Negative test result†
Transferrin saturation	39	93
Serum ferritin concentration	83	94

*Percentage of patients having a positive test result and lacking bone marrow hemosiderin.
†Percentage of patients having a negative test result and having bone marrow hemosiderin.

nant disease is also difficult to diagnose because these conditions may lead to hypochromic microcytic anemia and decreased percent transferrin saturation despite adequate amounts of reticuloendothelial iron.[8] Examination of bone marrow smears for stainable iron has proved to be a reliable means of detecting mild iron deficiency and of differentiating iron deficiency anemia and other forms of anemia.[8,9]

Using the absence of bone marrow hemosiderin as an index of iron deficiency we found that determinations of transferrin saturation and serum ferritin concentration were equally sensitive (Table I). However, the specificity of measuring the serum ferritin concentration was considerably higher than that of measuring the transferrin saturation because the latter gave falsely low results in many patients with chronic diseases whose reticuloendothelial iron stores were replete. The use of a lower threshold for an abnormal percent transferrin saturation, 16% rather than 20%, did not improve the efficiency of the test. Using the two tests together rather than measuring the serum ferritin concentration alone offered no advantage because the combination of tests had a lower specificity (Table I).

The predictive value of a positive test result for iron deficiency is related to the specificity of the test and to the prevalence of iron deficiency in the group of persons selected for investigation.[7] Since we found measuring the serum ferritin concentration to be superior to measuring the transferrin saturation only in specificity, the former is of most help in a group of persons with a low prevalence of iron deficiency.

When iron deficiency is virtually the only identifiable factor responsible for anemia, determination of the serum ferritin concentration has considerable advantage over determination of the serum iron concentration and the transferrin saturation because the results of the latter are often within normal limits in persons with mild iron deficiency. When iron deficiency anemia is associated with chronic infection, rheumatoid arthritis, widespread cancer, hematologic malignant disorders or liver disease, neither the transferrin saturation nor the serum ferritin concentration is a valid index of iron deficiency. In these conditions a shift of iron from erythrocytes to reticuloendothelial stores leads to a decreased serum iron concentration, a decreased transferrin saturation and an increased serum ferritin concentration. Nevertheless, a low serum ferritin concentration in these circumstances indicates iron depletion and a high serum ferritin concentration excludes it. In complicated clinical situations determination of the grade of bone marrow hemosiderin is the most reliable test for iron deficiency anemia.

The serum ferritin assay is less expensive than the other tests: in our hospital laboratory the technical cost of measuring the serum ferritin concentration was $1.50, whereas the cost of measuring the transferrin saturation was $2.50 and the cost of doing a bone marrow aspiration and preparing a smear for histologic examination was $15.

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