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Clinica Chimica Acta 353 (2005) 61–66

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Soluble transferrin receptor in hemochromatosis patients during phlebotomy therapy

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Received 26 July 2004; received in revised form 4 October 2004; accepted 7 October 2004

Abstract

Background: The monitoring of phlebotomies in hemochromatosis patients depends on iron status measured by ferritin and transferrin saturation (TS). However, in the presence of inflammation or liver injury, soluble transferrin receptor (sTfR) determination was proposed to replace ferritin for diagnosing iron deficiency (ID). The present study evaluated performances of sTfR for the prediction of iron deficiency in a large number of hemochromatosis patients under phlebotomy therapy.
Methods: We studied 52 patients undergoing therapeutic phlebotomies and obtained 2 samples from 37 patients. Biological parameters were determined before each phlebotomy began. Performances of sTfR and TS in the diagnosis of iron deficiency were compared, according to ferritin levels under 12 μg/l.
Results: Ferritin and TS were correlated with removed iron (r=0.473, p<0.005 and r=0.345, p<0.05, respectively) and sTfR was correlated with the decrease in hemoglobin levels induced by phlebotomies (r=−0.678, p<0.0001). Areas under Receiver Operating Characteristics (ROC) curves for sTfR and TS were not statistically different for prediction of iron deficiency and sensitivity/specificity of sTfR at 1.64 mg/l were 67/86%.
Conclusions: sTfR determination could be used to predict iron depletion induced by phlebotomies when ferritin is of limited interest, to avoid the appearance of anemia.

Keywords: Soluble transferrin receptor; Ferritin; Iron depletion; Phlebotomy; Hemochromatosis

1. Introduction

Hereditary hemochromatosis is an autosomal recessive disorder that affects 0.5% of the Caucasian population [1]. The treatment of hemochromatosis disorders consists of cumulative phlebotomies to

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doi:10.1016/j.cccn.2004.10.001

deplete iron stores during an induction stage and to prevent its reaccumulation during a maintenance stage. During the induction stage, iron removal is performed until ferritin levels and transferrin saturation (TS) decrease under 20 μg/l and 20%, respectively. Thereafter, phlebotomies are performed at regular intervals to maintain ferritin levels between 20 and 50 μg/l [2]. To avoid iron deficiency (ID) anemia, an adverse effect of therapeutic iron depletion [3], ferritin concentration and TS are currently used for monitoring therapy [2]. However, ferritin determination is of limited interest for the diagnosis of ID in the presence of inflammation or liver disease and different cut-off values are proposed for the diagnosis of ID, according to the gender [4] or the age of patients [5,6] and in patients with inflammation [7,8] or cirrhosis [9].

In the last few years, the determination of the soluble transferrin receptor (sTfR) has become routinely available. This soluble form of cellular transferrin receptor circulates in the plasma and reflects the total body mass of transferrin receptor [10,11]. In the absence of erythroid proliferation, an increase in sTfR level reflects tissue ID [10,12]. Since sTfR concentration is not influenced by inflammation or liver disease [13,14] or by age- or gender-related variations [11], it has been proposed to replace ferritin determination in the diagnosis of ID when confounding factors of ferritin are present [13,14].

The present study evaluated sTfR as a marker of iron depletion, defined as ferritin values under 12 μg/l, induced by phlebotomies in a large population of hemochromatosis patients and its potential diagnostic value in the monitoring of phlebotomies, compared to classical parameters.

2. Methods

2.1. Patient characteristics

The patient population consisted of 52 consecutive male patients who underwent phlebotomies in the Department of Internal Medicine, Pitié-Salpétrière Hospital. The inclusion criteria was any hemochromatosis male patient who was included in the phlebotomy planning at the beginning of the study. They were already diagnosed as hemochromatosis patients at the beginning of the study, according to clinical criteria and according to a TS over 60% on repeated measurements [15]. Blood samples were taken after informed consent, and determination of parameters of the iron status was performed before each phlebotomy began. Five patients with fever or biochemical signs of inflammation (orosomucoid levels >1.2 g/l and/or C-reactive protein levels >4 mg/l) were excluded from the study to avoid interferences with the interpretation of ferritin concentrations since we defined iron depletion on the basis of ferritin values less than 12 μg/l [16].

2.2. Analytical methods

Soluble transferrin receptor, ferritin, transferrin, orosomucoid, C-reactive protein and haptoglobin were determined by immunonephelometry in serum samples on a nephelometer BN2 (Dade Behring, Marburg, Germany). Soluble transferrin receptor was determined using a mouse monoclonal antibody and interday reproducibility of the assay gave total coefficient of variation of less than 3% for concentrations ranging from 0.14 to 4.40 mg/l. Standards for transferrin determination were calibrated against the CRM 470/RPPHS [17]. Iron determination was performed by colorimetry, using the ferrozine method, and creatinin and Alanine Amino-Transferase (ALT) were routinely determined on an Integra 400 (Roche Diagnostics, Meylan, France). Transferrin saturation was calculated according to the formula: [iron (μmol/l)×100/transferrin (g/l)×0.25]. Total blood count and reticulocyte counts were determined in whole blood samples on a Technicon H3 (Bayer Diagnostics, New York, USA).

The determination of the C282Y and H63D mutations were already available at the time of the study and have been performed by Restricted Fragment Length Polymorphism-PCR using the published primer sequences of Feder et al. [18].

2.3. Calculation of iron removed during the study

In 37 of the 52 included patients, 2 samples at least were obtained during the period of the study. A volume of 250–500 ml of blood was removed once a week to once per 42 weeks according to the stage (depletion or maintenance) of therapy. The amount of iron removed with each phlebotomy was calculated