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Should a Search for Iron Deficiency be Part of the Regular Screening in All Patients, whether Anemic or not?

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Introduction

In the Symphonie Fantastique written in 1830 by Hector Berlioz, in all five movements, a certain obsessional theme - a leitmotif - keeps coming back again and again in different guises. But even though it may sound different in each of the five movements, and is played by different instruments, it is basically the same.

There is a striking resemblance between this and a leitmotif that runs through many medical conditions- iron deficiency (ID). It may cause different signs and symptoms in different people [1,2], including anemia, weakness, frailty, headache, irritability, shortness of breath, tiredness, reduced exercise tolerance, a tendency to fall, lack of cognitive function, restless legs syndrome, depression, worsening of Quality of Life and increased hospitalizations and morbidity. And it may worsen Congestive Heart Failure (CHF) [3-6]. It may also present with or without anemia.

There are two different types of ID-absolute ID with low serum iron, low % Transferrin Saturation and low serum ferritin (associated with low total iron stores), or functional iron deficiency with low serum iron, low % Transferrin Saturation and elevated serum ferritin (this combination suggesting normal or high body iron stores- the so-called Anemia of Chronic Disease [7,8].

In absolute iron deficiency there is an actual reduction in body stores of iron, and the serum ferritin levels are generally less than 30 ug/l. It can be caused by poor nutrition with reduced iron intake, menstrual blood loss, pregnancy, gastrointestinal blood loss from many causes including bleeding from Non Steroidal Anti Inflammatory Agents, antiplatelet therapy or oral anticoagulation, stomach or duodenal ulcers, gastritis, angiodysplasia , inflammatory bowel diseases, benign or malignant tumors of the stomach or bowel or malabsorption from many causes including celiac disease .

The iron deficiency can also be functional iron deficiency in which case the iron stores are normal or elevated but iron is neither absorbed or released from storage areas. Absolute Iron deficiency, can bedefined as a serum ferritin of <30 ug/l . One current definition of functional ID is either a serum ferritin of <100 ug/l or a serum ferritin of 100-299 ug/l and a %Transferrin Saturation (%TSat) (serum iron divided by serum transferrin and this multiplied by 100%) <20%. It is caused by the release of cytokines from inflamed tissues which cause the release of Hepcidin from the liver. The inflammatory state may be caused by chronic infection, cancer, renal failure, acute or chronic Congestive Heart Failure (CHF), Chronic Obstructive Lung Disease (COPD), inflammatory bowel disease, rheumatoid arthritis and even obesity, diabetes and exercise [3-5,7,8]. This protein, Hepcidin, reduces the effect of the protein ferroportin, thus preventing its' ability to absorb iron from the gut and also to release of iron from iron stores in the liver and macrophages [7,8]. This lowers iron levels in the blood and therefore reduces iron delivery to the bone marrow causing an iron deficiency anemia. ID is easily and safely treatable with oral or intravenous (IV) iron with few side effects [1-6,9-14] and can be recognized both in anemic and non anemic patients by the simple blood tests shown above [1,2].

Correction of ID has improved the many symptoms mentioned above in people with Acute or Chronic CHF [3-6] (where it has also been shown to be very cost effective in improving endurance and Quality of Life [15,16]), Chronic Renal Failure (CRF) [9-14], Inflammatory Bowel Disease (IBD) [17], anemia related to chemotherapy in cancer patients [18,19], rheumatoid arthritis [20], restless legs syndrome [21], athletic performance [22-24]including, in a recent meta-analysis, improved maximal and submaximal exercise performance in women of reproductive age [24], premenopausal women whether anemic or not [25,26], pregnant women [27-29], post partum women [28,29], infants and young children [30], and pulmonary hypertension [31], and has reduced transfusion requirements when given before surgery in many different kinds of surgical procedures [32]. ID is also seen more often in obesity [33], diabetes [34], old age [35] stroke [36], Peripheral Vascular Disease [37] and Chronic Obstructive Pulmonary Disease (COPD) [38,39] but adequate randomized controlled intervention studies with iron in these latter conditions have, to our knowledge, not been published. The increased risk of stroke and vascular disease seen with ID could be partly due to the thrombocytosis and increased platelet aggregation caused by the iron deficiency [36,37].

Treatment of iron deficiency can be done with either oral or Intravenous (IV) iron. In conditions which demand more rapid correction because of more severe symptoms, IV iron should be used whereas if the condition is mild, oral iron can be used, although it is often not tolerated because of gastrointestinal symptoms.

However the diagnosis of iron deficiency is often not sought after in all the above conditions. We examined the records of 76 consecutive patients admitted to one of our nine hospital medical wards with a primary diagnosis of CHF [40]. We found that anemia (defined as a Hb of <12 g/dl) was found in 42/76 patients (55.3%). An iron workup was only performed in 14.7% of the non anemic and 23.8% of the anemic patients. ID was defined as either a serum ferritin of <100 ug/l or a serum ferritin of 100-299 ug/l and a %Transferrin Saturation (%TSat)<20%. ID was found in 90% of the anemic and 60% of the non anemic patients in whom there was an iron workup. Only 6/42 (7.1%) of the anemics were taking oral iron and only 1/42 (2.4%) were taking IV iron at the time of admission. In those with a complete iron workup 11/15 received oral or IV iron at the time of discharge whereas in those without any iron workup only 1 (1.8%) received iron at discharge. We

concluded that ID is extremely common in hospitalized CHF patients whether anemic or not but is usually not sought after by most physicians at the time of admission. The fact that, in our study, about 3/4 of those with a complete iron workup received oral or IV iron therapy at discharge suggests that doctors who investigate for iron deficiency and find it are usually willing to treat it if it is found- an optimistic note and the motivation for this paper.

In another recent study of COPD patients [39] we examined the hospital records of all patients hospitalized in our hospital with a primary diagnosis of exacerbation of COPD to assess the investigation, prevalence, and treatment of ID. In this same study we also examined retrospectively the records of 12 anemic COPD outpatients (anemia: Hb <12 g/dl) who had been treated in our nephrology clinic with the combination of ESAs and IV iron given once weekly for 5 weeks. Initially and one week after treatment we measured the hematological response and the severity of dyspnea by Visual Analogue Scale (VAS). Of 107 consecutive patients hospitalized with exacerbation of COPD examined, 47 (43.9%) were found to be anemic on admission. Two (3.3%) of the 60 non-anemic patients and 18 (38.3%) of the 47 anemic patients had a full iron workup with serum iron, %Transferrin Saturation (%TSat) and serum ferritin measured. All 18 (100%) anemic patients had ID by our criteria (the same criteria as in the previous study), yet none had oral or IV iron subscribed before or during hospitalization, or at discharge.

In the intervention outpatient study, ID was found in 11 (91.7%) of the 12 anemic ambulatory COPD patients. With Erythropoiesis Stimulating Agents and IV iron treatment the mean Hb increased from 9.72 ± 1.16 to 12.29 ± 1.09 g/dl and the VAS scale increased from 2.20 ± 1.13 to 8.45 ± 0.92 p = 0.002. The VAS was highly correlated with the change in Hb.

It is important to stress that many patients with iron deficiency are not anemic and physicians will often not measure iron parameters unless anemia is present. This in our opinion is a serious error. Many patients with severe symptomatic iron deficiency will be missed.

Conclusion

Iron deficiency, whether absolute or functional is exceedingly common, yet it is often not sought after and, if it is found, it is often not treated. But treatment with oral or intravenous iron can improve the anemia, fatigue, exercise tolerance and endurance, cardiac function, cognitive function and quality of life in a great many conditions. It is an unmet challenge for physicians. Measurement of serum iron, Transferrin, percent Transferrin Saturation, and serum Ferritin should, in our opinion, be part of the standard workup of all patients- with or without anemia, since many iron deficient patients are not anemic. This includes patients in both family practice and on admission to hospital for any cause. If iron deficiency is discovered its' cause should be looked for and, when discovered, should be treated. The improvement of the patient with ID with oral or IV iron will often be rapid, striking and gratifying both for the patient and for the treating physician. Few conditions in medicine are as common, as easily diagnosed and treated, and can improve the quality of life as much as iron deficiency.

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