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Serum ferritin and other iron indices in adult Nigerians with chronic renal failure — Review of management of anaemia

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Summary

Iron studies were carried out in twenty five adult male and female patients with chronic renal failure and thirty one "healthy" individuals as control.

Results showed moderately severe anaemia in all the patients with a mean haemoglobin concentration of 7.4mg/dl (range 6-9.8 gm/dl). Transferin saturation of 28.8% in the patients was similar to the value of 29.2% in the control group. However, the mean serum ferritin value of 610µg/L in the patients was significantly higher than the corresponding values of 165µg/L and 58µg/L in the control groups respectively.

In patients with chronic renal failure, three out of ten bone marrow aspiration showed no stainable iron, and in five patients, iron was grossly increased with corresponding increases in serum ferritin values. In addition, four of the five patients had severe megaloblastic changes in the marrow.

Resume

Etudes de fer etaent fait sur 25 hommes et femmes souffrant de detauts renal chronique et 31 individus en bonne sante comme temions. Les resultants montrent que tous les patients avec une concentration doyenne d'hemoglobine de 7.4gm/dl (range 6-9.8gm/dl) etaient severement anemique. La saturation de transferrin de 28.8% des patients etaient comparable de valeur de 29.2% dans le groupe des temoins. Mais la valeur moyenne de ferritin dans le serum des patients etaient 610µg/L qui etait beaucoup plus elever dans les groupes de temoins, valuer de 165µg/L et 58µg/L respectively. Trois sur dix patients n'avaient pas de fer (stainable) dans daspiration de moell et 5 patients demonstraient une augmentation de fer avec augmentation parallel de valeur de ferritin dans leur serum. En plus 4 sur 5 patients montraient des profonds changements megaloblastiques dans leur molles.

Introduction

Previous workers have described the anaemia of chronic renal failure and have ascribed the causative mechanisms as follows: (a) decreased erythropoeitin production[1,2]; (b) retained inhibitors and toxic metabolites that suppress erythropoeisis[3,4,5,6]; (c) shortened red cell life span[7,8,9]; (d) blood loss related to dialysis, frequent blood testing and occult loss[10,11,12]; (e) loss of folate and other water-soluble vitamins during haemodialysis[13] and (f) blood loss resulting from the qualitative platelet defect present in uraemia[14]. Erythropoeitin deficiency is a major mechanism of this anaemia. Ninety percent of erythropoeitin is made normally in the kidney and only 10% is produced in the liver[15]. Figures obtained by using the more modern radio-immunoassay method to measure purified urinary and serum erythropoeitins respectively, showed that there is relative erythropoeitin deficiency in chronic renal failure[16].

In some parts of the world, serum ferritin levels, serum iron concentration, total iron binding capacity, percentage transferrin saturation and bone marrow iron availability have been used to diagnose iron deficiency anaemia in patients with chronic renal failure[17,18,19]. Also serum ferritin levels, plasma iron values and bone marrow iron estimations have been studied in other clinical conditions unrelated to renal diseases in the diagnosis of iron deficiency anaemia and subsequent management [20,21,22, 23,24]. The present study extends the haematological investigations of iron deficiency to patients with

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chronic renal failure and who are also on chronic haemodialysis.

Subjects and methods

Fifty six adult Nigerian males and females were the subjects of this study. They were made up of 25 patients with chronic renal failure (16 males and 9 females) and 31 "healthy" individuals (17 males and 14 females) who constituted the control group.

Patients with Chronic Renal Failure (CRF):

All twenty five patients were attending the hypertension clinic at the University College Hospital, Ibadan, Nigeria. All the patients were on chronic maintenance haemodialysis using the coil dialyzer and Extracorporal batch Tank System DM 201. The majority of the patients were severely hypertensive.

Control subjects:

These comprised of 15 University College Hospital, Ibadan workers including doctors, nurses and other paramedical staff and 16 others from outside the hospital mainly teachers at an Ibadan primary school.

Method

The packed cell volume (PCV) and the haemoglobin concentration were determined by the method of Dacie and Lewis[25]. The serum iron concentration and the total iron-binding capacity (TIBC) were estimated by the method of Williams and Conrad[26]. Serum Ferritin concentration was measured using the immunoradiometric assay (IRA) [27]. The bone marrow aspirations were obtained from the sternum and stained for cellular morphology using May-Grunwald-Giemsa stain and for iron by Perl's prussian blue stain. Iron scores were done blindly by one of us (O.A.O.). The presence of iron was graded from 1 to 3 according to the method of Sorbie, Olatunbosun and Corbett[28]. A control iron stain (from a sickle cell anaemia patient with over transfused haemosiderosis) was run with the batch. The biochemical investigations were carried out using the method of Varley[29]. Results were analysed using the student's t test.

Results

Table 1 shows the age, and some other haematological values. The mean age of the patients (32.1 ± 3.2 years) was not significantly different from that of the control (30.9 ± 1.2 years).

Haemoglobin and haematocrit values

In the patients, the mean values of haemoglobin concentration and haematocrit level (7.4gm/dl and 24%, respectively) were significantly lower than the corresponding values in the control group (14.5gm/dl and 44% in males, and 12.5gm/dl and 39% in females respectively).

Table 1: Haematological parameters in chronic renal failure and control group

	Age in yrs.	Haemoglobin gm/100ml	Haematocrit percentage	Serum iron µg/100µl	Total iron binding capacity µg/100ml	Transferin saturation %	Serum ferritin µg/L
Patients (25)	32.1 ± 3.2	7.4 ± 0.9	24%	72.1 ± 15.0 20 - 135	235 ± 18	28.8 ± 1.9	610 ± 25.4 (20 - 1000)
Control (31)	30.9 ± 1.2	M = 14.5 ± 2.1 F = 12.5 ± 0.8	44% 39%	101.5 ± 20 (80 - 150)	350 ± 25	29.2 ± 2.1	M = 165 ± 12.9 F = 58 ± 5.2

Serum iron, total iron binding capacity and transferrin saturation

The mean serum iron level among the patients 72.1μg/100ml (range 20-135μg/100ml) was significantly lower than the corresponding values for the controls 101.5μg/100ml (range 80-150μg/100ml) ($P < 0.01$). The mean TIBC values, 235μg/100ml for the patients and 250μg/100ml for the control group were not significantly different. The transferrin saturation 28.8% in the patients and 29.2% in the control group were very similar.

Serum ferritin levels

Serum ferritin was evaluated in 10 of the 25 patients and all of the 31 controls. In the patients, serum ferritin level varied widely (20-1000μg/L) with a mean of 610.4 ± 25.4. In 3 of the patients, values were 1000 ± μg/L and in two others values were 700μg/L and 790μg/L respectively. Among the control, there were skewed distribution with the mean values of 165.0 ± 12.9μg/L in male and 58.0 ± 5.2μg/L in female.

Bone marrow studies

10 patients who had serum ferritin estimation also had their bone marrow studied. There was depression of all the cellular components in all the marrow aspirates, — this depression was more marked in the erythroid series, than in the myeloid and megakaryocytic series. Four of the 10 patients (3 males and 1 female) on maintenance haemodialysis had evidence of severe megaloblastosis, and markedly increased values of serum ferritin after having had 24, 16, 36 and 42 units of packed cells transfused respectively.

Iron stores and serum ferritin values

Of the 10 marrow aspirates done, 3 had no iron, 2 had normal iron and 5 had excess iron. All the five patients with grossly increased iron in the marrow had serum ferritin values above 700μg/L and in 3, the values were greater than 1000μg/L. In the 3 patients with no iron in the marrow, the serum ferritin values were 29, 45 and 200μg/L respectively, with a mean of 91.3μg/L. This mean value was significantly lower than the mean of 610μg/L in those with normal iron, and 935μg/L in those with excess iron.

Biochemical values

Biochemical values including serum urea and serum creatinine were evaluated in all the patients. There was gross derangement of biochemical values in all the patients compatible with chronic renal failure. The pre and host haemodialysis mean blood urea values were 194.7 ± 13mg/100ml and 84.8 ± 9.8mg/100ml while the corresponding values for serum creatinine were 17.3 ± 1.6mg/100ml and 8.7 ± 0.8mg/100ml respectively.

Discussion

Anaemia of chronic renal failure is multifactorial. Esbach[1] discussed at length the pathophysiology of anaemia in chronic ronal failure. Among the factors mentioned are (a) erythropoeitin deficiency; (b) bone marrow inhibition by inhibitors of erythropoeisis. Such inhibitors are reported to blunt or even block the effect of erythropoeitin on bone marrow tissue. The infusion of erythropoeitin-rich plasma from a patient with aplastic anaemia into several patients with advanced renal failure and anaemia failed to elicit a reticulocytosis[30]. Also, shortened red-cell survival with red-cell haemolysis contribute to anaemia of chronic renal failure. Most radio-isotope studies using ^{51}Cr, ^{31}Df, ^{32}P or ^{14}C cyanate[33] have confirmed the presence of mild haemolysis. Moreover, significant blood loss is known to occur in patients with chronic renal failure which leads to anaemia[12]. The causes of blood loss in these patients are associated with qualitative platelet defect that develops in azotaemic patients[14,34,35]. This platelet defect includes decreased platelet Factor 3 activity[36], decreased platelet levels of thromboxane A_2 [27] and increase in prostacyclin (PGI_2); an inhibitor of platelet aggregation, and sub-optimal Factor VIII: Von Willibrand complex activity[38].

In this study, anaemia was a constant finding in all the 25 patients with CRF. The anaemia was severe with haemoglobin concentration of 7.4gm/100ml. This degree of anaemia was similar to that observed by others in a study of 44 patients[17]; in another study of children and teenagers undergoing maintenance haemodialysis[39] and, more recently, in a detailed well-discussed single case report[1].

Serum ferritin, bone marrow iron and megaloblastosis

In this study 3 of the 10 bone marrows, studied had no iron, with corresponding lower serum ferritin values than those with normal or increased iron. This agrees with the observation of a previous group[17] who found no stainable iron in four out of 44 patients and 'low' serum ferritin in 3 of them. Low serum ferritin values of 13, 29 and 33μg/L were reported in these 3 patients with absent marrow iron. In the report by another group[18] each of the 5 patients with nil or trace marrow iron had serum ferritin levels of less than 35μg/L. In our study, a positive correlation ($P < 0.002$; $r = 0.48$) was observed between marrow iron stores and serum ferritin levels. Similar correlations have been observed previously. In the study of Hussein *et al.* [17] it was also found that the serum ferritin levels, in patients with 0, 1+, 2+ and 3+ iron stores were 42, 387, 1200 and 3224μg/L respectively. Another group[19] also reported mean values of 110, 551 and 2069μg/L in patients with minimal, moderate and markedly increased marrow haemosiderin respectively. Megaloblastic erythropoeisis was found in 5 out of the 10 marrow aspirates of our patients. All five patients were on maintenance haemodialysis and excess iron was found in their marrow. This agrees with the findings of other observers[13]. Our patients with chronic renal failure have evidence of iron deficiency and megaloblastic erythropoeisis. These findings are similar to previous reports[40,41]. Some workers have suggested loss of blood during haemodialysis as one cause of iron deficiency, and removal of folate and other water soluble vitamins during dialysis as a cause of megaloblastic erythropoeisis[13].

Management of haematinics deficiency in anaemia of CRF

The management of anaemia in CRF has undergone revolutionary changes lately. Traditional treatment of this anaemia included administering androgens and the use of blood transfusion if hypoxic symptoms continue. To prevent megaloblastosis, 1 mg of folic acid is given usually orally to offset losses of this water-soluble vitamin during haemodialysis. In our study there was evidence of megaloblastic erythropoeisis probably due to folate deficiency. It has become prudent to administer folic acid to all patients with CRF who are undergoing haemodialysis, as in other centres.

Monitoring iron state

It has been suggested that it is important to determine clearly the base-line iron state of patients with CRF for purposes of proper management of iron deficiency anaemia[42]. It has also been stated that in patients initially deficient in iron, only sub-optimal rise in haemoglobin concentration can be expected to occur with iron treatment intravenously[43] or orally[44]. Even in the management of the anaemia with recombinant human erythropoeitin, inadequate iron limits the full response of the haemoglobin concentration to this latest management modality [42,45,46]. Indeed, the advent of recombinant human erythropoeitin therapy, a potent therapeutic stimulus of erythropoeisis requires large quantities of available iron for maximum haemoglobin response. Thus patients who start with repleted iron stores rapidly deplete their iron stores during this treatment[1,42,43]. It has been stated that in uraemic patients with haemoglobin concentration of less than 10g/100ml, there is certain benefit from erythropoeitin treatment[42]. In a large multicentre trial of erythropoeitin in the United States and Europe, 95-98% of the patients treated responded positively[47].

In our study, two groups of patients are identifiable. In the small group with haemoglobin concentration of 7.4 ± 0.9g/100ml, many have low values of serum iron and serum ferritin with severely depleted bone marrow iron stores. The second larger group have adequate iron in the bone marrow and normal to raised serum ferritin with normal iron stores in the face of low haemoglobin levels.

It will be expedient firstly to correct the iron deficiency of the first smaller group shown to be iron deficient by administering oral or intravenous iron[44,45] and then monitor for increase in blood iron indices, including raised reticulocyte count. The second larger group with anaemia and iron repletion (available bone marrow iron, increased transferrin saturation and increased serum ferritin) need the most current management of erythropoeitin therapy to activate their suppressed haemopoeitic tissue. The anaemia of chronic renal failure is now fully correctable with erythropoeitin[1,42,45]. The benefits to patients are fully documented and include enhanced physical fitness and appetite[48], relief from dysgensia, increased daily activity and improved sleep habits. Conversely, potential complications of treatment with erythropoeitin such as hypertension [49,50], thrombosis of the arteriovenous fistula[51,52],

"flu-like" symptoms[51] and increased plasma potassium concentrations[50] will all have to be carefully monitored during the introduction of this modern, revolutionary and universally acclaimed management of anaemia of chronic renal failure.

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