
Serum Erythropoietin in Severely Malnourished Infants

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Abstract:

Anemia has been well documented in protein energy malnutrition (PEM), but the role of erythropoietin (EPO) in its production remains controversial. This work was carried out on 30 severely malnourished infants and 10 age and sex matched healthy controls. Anemia was moderate among all the malnourished cases who also had low serum ferritin levels. Kwashiorkor and marasmic kwashiorkor cases had more fragile red cells than marasmus and control infants did. Although EPO production was increased and appropriate for the degree of anemia in cases of PEM, there was no concomitant significant increase in the absolute reticulocyte count. So, anemia of PEM could be attributed to abnormal erythropoiesis and increased red cell osmotic fragility but not to EPO deficiency.

Introduction:

Hematological changes are an invariable accompaniment of protein energy malnutrition (PEM) and anemia has always been a constant feature. Although protein deficiency is the main problem in PEM, iron deficiency and metabolic changes of the red cells may influence the associated anemia. Also, vitamins, trace elements, and infection play subsidiary and interactive role.^(1,2) The role of erythropoietin (EPO) in the anemia of PEM remains controversial.⁽⁴⁾ It has been proposed that it may be due to reduced production of EPO as a consequence of protein deficiency or due to deficiency of energy- probably mediated through decreased levels and sensitivity to triiodothyronine.⁽³⁾ Others reported normal or even elevated EPO levels in severe PEM. They explained the failure of raised serum EPO levels to elicit an adequate increase in erythropoiesis by either decreased responsiveness of the erythropoietin – sensitive cells in the bone marrow or ineffective erythropoiesis.⁽⁴⁾ The aim of this work was to assess the state of anemia and to correlate serum erythropoietin hormone levels & the severity of anemia in infants suffering from severe PEM.

Subjects and methods:

The study was conducted on 40 infants whose ages ranged from 6 to 15 months. They included 30 severely malnourished cases divided into three equal groups (kwashiorkor, marasmic kwashiorkor and marasmus) and 10 normally growing, age and sex matched infants as control group. All the infants were subjected to thorough clinical examination, to chest radiography to exclude pulmonary infection and to laboratory investigations including:

- 1- Urine & stool analysis
- 2- Peripheral venous blood samples were obtained at 8 AM⁽⁵⁾ for estimation of:
 - Serum erythropoietin level by radioimmunoassay.⁽⁶⁾
 - Serum ferritin and protein levels.⁽⁷⁾
 - Osmotic fragility test by extrapolating the concentration of saline causing hemolysis of un-incubated red blood cells.⁽⁸⁾
 - Complete blood count by Coulter counter.⁽⁹⁾ In this study, the degree of anemia was considered to be: mild at Hb levels 10-<11 gm/dl; moderate at Hb levels 6-<10 gm/dl; severe when Hb levels were <6 gm/dl.
 - Calculation of:
Mean corpuscular volume (MCV) in FI =
$$\frac{\text{Hematocrite (Ht)\%}}{\text{RBC counts (in millions)}} \times 10$$

Mean corpuscular hemoglobin concentration in g/dl =
$$\frac{\text{Hb (g / dl)}}{\text{Hb\%}} \times 100$$

Absolute reticulocyte count = Observed reticulocyte count (%) x RBC count = cells x 10⁹/L.

Results:

- All the malnourished cases included in this work were anemic (Hb<11 gm/dl) . They had significantly lower levels of Hb, Ht and RBC counts than control infants. (table I)
- Kwashiorkor and marasmic kwashiorkor cases had significantly more fragile red cells than cases of marasmus and control infants. (table II)
- Although malnourished cases had a significantly higher mean of serum EPO levels

than controls, the difference in the absolute reticulocyte counts was not significant.

- Serum ferritin levels were significantly lower among the malnourished cases. Also, Kwashiorkor and marasmic kwashiorkor cases had significantly lower total serum protein (TSP) levels than marasmus and control infants. (table III)

- There was significant inverse correlation between both logarithmic serum EPO levels and both; Hb and Ht values among the studied malnourished cases but no significant correlation was detected between Log EPO and either absolute reticulocyte and TSP levels

(p >0.005). (figures 1,2).

Table I: Peripheral blood parameters among the studied infants

	Control (n=10) X±SD	Marasmus (n=10) X±SD	M. kwashiorkor (n=10) X ±SD	Kwashiorkor (n=10) X ±SD	F test values & sites of significance
Hb level (gm/dl)	12.6 ± 1.0	9.1±1.1	9.1±1.4	9.0±1.2	22.9* (1,2)(1,3)(1,4)
RBC count (x10 ⁶ /cmm)	4.9 ± 0.6	3.2±0.4	3.4±0.4	3.2±0.8	18.9* (1,2)(1,3)(1,4)
Hct values (%)	38.0±3.3	28.6±4.5	29.1±4.8	29.6±4.5	10.77* (1,2)(1,3)(1,4)
MCV (FL)	78.6±4.4	88.4±7.6	85.3±7.2	97.4±29.9	2.37
MCHC (gm/dl)	33.2±0.6	32.1±3.9	31.5±1.9	30.5±2.4	2.05
Abs. Reticulocyte count (cellx 10 ¹² /L)	0.055±0.02	0.048±0.05	0.064±0.04	0.055±0.05	0.25

* Significant at 1% level

Table II: Osmotic fragility test among the studied infants.

	Control (n=10) X±SD	Marasmus (n=10) X±SD	M. Kwashiorkor (n=10) X±SD	Kwashiorkor (n=10) X±SD	F test value & sites of significance
Osmotic fragility test (%)	0.41±0.07	0.37±0.03	0.27±0.05	0.29±0.34	19.35* (1,3) (1,4)(2,3)(2,4)

*Significant at 1% level

Table III: Serum EPO, ferritin and total protein levels.

	Control (n=10) X±SD	Marasmus (n=10) X±SD	M. Kwashiorkor (n=10) X±SD	Kwashiorkor (n=10) X±SD	F test values & sites of significance
Serum EPO # (mIU/ml)	80.0	64.91	55.95	17.77	14.16* (1,2)(1,3)(1,4)
Serum ferritin (ng/ml)	56.8±6.6	21.1±24.4	15.8±7.9	20.0±5.26	19.94* (1,2)(1,3)(1,4)
Total serum protein (gm/dl)	7.02±0.4	6.5±0.7	3.54±0.6	3.8±0.8	83.77*(1,3) (1,4)(2,3)(2,4)

Geometric mean was calculated instead of arithmetic mean.

* Significant at 1% level.

Fig. 1: Correlation between serum EPO level & Hb levels

Fig. 2: Correlation between serum EPO level & Hct values

Discussion:

The moderate anemia observed among the studied malnourished cases was in agreement with the previous reports from Egypt.⁽⁹⁾ Some investigators recorded higher levels of hemoglobin that can be explained by different dietetic patterns, associated infections or parasitic infestations in different localities.⁽¹⁾ The decreased iron stores was reflected by the lower ferritin levels estimated in the malnourished cases. This iron deficiency was not so severe to reach the depletion stage (<10 ng/ml) that causes the characteristic hypochromia of iron deficiency. This was in accordance to the report that iron stores become depleted during nutritional rehabilitation and the period of catch up growth due

to increased erythropoietic activity. ^(1,10,11) The hypochromia observed in few of the malnourished cases which had no corresponding iron depletion could be explained by defective iron utilization due to infection and/or reduced serum proteins that hinder hemoglobin synthesis.

In spite of the suggestion that iron deficiency is the major cause of PEM-associated anemia, the tendency of MCV to be increased could be attributed to concomitant deficiency of other nutrients like folate, vitamin E & B₁₂ and ascorbic acid. ^(9,12) Also, decreased RBC osmotic fragility observed in kwashiorkor and marasmic kwashiorkor cases was in agreement with other investigators who attributed it to abnormalities of the red cell membrane lipids that could be due to hepatocellular

derangement met with in kwashiorkor. ^(13,14) The production of EPO hormone by the malnourished cases was not only normal or even increased but appropriate to the degree of the present anemia which was manifested also by the inverse correlation between Log serum EPO and both; Hb and Ht values. Moreover, the lack of correlation between serum EPO and protein levels suggested that protein deficiency had no effect on the production of this hormone in PEM. These results were in accordance to many investigators who reported similar levels of EPO in anemic malnourished cases and others with comparable degree of anemia whatever its cause other than anemia of renal disease. ^(2,4,15) In contrast, some workers claimed decreased EPO production to be the main cause of PEM –associated anemia. The decreased production was explained by deficiency of proteins and/or calories and decreased sensitivity to triiodothyronine. ^(3,16)

We suggest that infants with PEM suffer from impairment of erythropoiesis evidenced by insignificant rise of reticulocyte counts despite persisting anemia. Also, the lack of correlation between Log serum EPO and the absolute reticulocyte count -a simple index of erythropoietic activity- indicate that EPO is not the major determinant of effective erythropoiesis. This was in agreement with the other workers who claimed decreased responsiveness of EPO-responsive cells and/or ineffective erythropoiesis to be the cause of failure of raised serum EPO levels to elicit an adequate increase of effective erythropoiesis. ^(4,17) Accordingly, we concluded that PEM- associated anemia could be attributed to abnormal erythropoiesis and increased red cells osmotic fragility, but not to erythropoietin hormone deficiency.

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