

Anemia in Rickets Due to Vitamin D Deficiency*

Şinasi Özsoylu, M.D.**/

Ghulam Mohammed Riaz, M.D., B.S.D.C.H.,***/

Enver Hasanoglu, M.D.****

Vitamin D-deficiency rickets is occasionally seen in some developed countries,^{1,2} but it is more prevalent in this part of the world.³⁻⁷ In spite of plentiful sunlight, rickets is still an important clinical problem in several developing countries. Anemia is not a rare associated finding in these children and most likely is due to other deficiencies. There have been several studies for the classification of the pathogenesis of anemia associated with vitamin D deficiency rickets,⁸⁻¹² but it has not been established whether the anemia is related to rickets or not.

The purpose of this study was to find out any relationship, in general, between anemia and rickets and correlation between serum inorganic phosphorus level with hemoglobin concentration in children with rickets. The latter correlation seemed to be important since Card and Brain¹³ postulated that the "anemia" of childhood was the response to hyperphosphatemia in this age group.

Materials and Methods

Two hundreds children with rickets diagnosed by X-ray examination at Hacettepe Children's Hospital were analyzed and their results were compared with those of 100 children, seen during the same period, who showed no X-ray evidence of rickets. The ages of the children in both groups ranged between 1.5 and 24 months and the mean age was 7.3 (S. D. $\pm$ 3.9) and 5.7 (S. D. $\pm$ 3.5) months in the study and control groups (Figure 1).

* From Hacettepe University, Faculty of Medicine, Department of Pediatrics and Hacettepe Children's Hospital Medical Center, Ankara, Turkey.

** Professor of Pediatrics and Hematologist.

*** Cento Fellow in Pediatric Hematology.

**** Associate in Pediatrics.

Hemoglobin (Hb) and Hematocrit (Hct) values were obtained by cyanmethemoglobin and microhematocrit methods and the blood smear was evaluated with Wright stain. Serum calcium (Ca), phosphorus (P) and alkaline phosphatase levels were determined by the methods of Clark and Collip,¹⁴ Fiske and Subborow¹⁵ and Bodansky,¹⁶ successively.

Results

Hb and Hct values in the study group ranged between 4.55 and 15.32 g/dl with the mean of 10.35 g/dl and 17 to 47 % with the mean of 32.4 %, respectively. When these values were compared with those of the controls no statistical difference was found (Table II), and the prevalence of anemia (Hb < 11 g/dl in this age group) with 59 and 55 % in two groups were not different either.

Serum inorganic phosphorus values, ranged from 1.5 to 9.4 mg/dl (mean of 4.15 mg/dl) and from 2.1 to 9.2 mg/dl (mean of 4.56 mg/dl) in both groups, being significantly lower in patients with rickets ($P < 0.05$ / Table II). The rickets cases were further studied and grouped into 3 categories according to serum phosphorus levels.

- a. Normophosphatemic rickets in which the serum P levels ranged between 3.6 and 6 mg/dl.
- b. Hypophosphatemic rickets in which the serum P levels ranged between 1.5 and 3.5 mg/dl.
- c. Hyperphosphatemic rickets in which the serum P levels ranged between 6.1 and 9.4 mg/dl.

The Hb, Hct and serum P values were also compared between these groups. The serum P levels were found significantly different between groups, as expected ($P < 0.001$), but the Hb and Hct values were not found to be significantly different between groups ($P > 0.05$ / Table III).

Keeping in view the influence of age on serum P levels, the cases of rickets and controls were further subdivided into 3 groups to determine any correlation between P and Hb values:

- a. Those who were less than 3 months,
- b. Those between 4 and 6 months,
- c. Those who were more than 7 months.

Hb, Hct and serum P levels were not found significantly different in any age group except in the one with 4 to 6 months of age, in which only the serum P differed significantly in the study and control cases ($P < 0.01$ / Table IV).

TABLE II
COMPARISON OF HEMOGLOBIN, HEMATOCRIT AND SERUM PHOSPHORUS LEVELS
BETWEEN RICKETS AND CONTROLS

Subject	Number	Hemoglobin g/dl		Hematocrit value (%)		Serum phosphorus mg/dl	
		Range	Mean (S.D.)	Range	Mean (S.D.)	Range	Mean (S.D.)
Rickets	200	4.55-15.32	10.35±1.98	17-47	32.40±5.52	1.5-9.4	4.15±1.44
Controls	100	6.00-14.87 P > 0.05	10.53±2.09	19-44 > 0.05	32.07±6.12	2.1-9.2 < 0.05	4.56±1.38

TABLE III
COMPARISON OF HEMOGLOBIN, HEMATOCRIT AND SERUM PHOSPHORUS LEVELS
BETWEEN THREE TYPES OF RICKETS

Type of		Hemoglobin level (gm/dl)		Hematocrit value (%)		Serum phosphorus level (mg/dl)	
Rickets	Number	Range	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range	Mean $\pm$ SD
Normophosphatemic	91	5.96-14.87	10.26 $\pm$ 1.94	19-42	32.31 $\pm$ 5.54	3.6-6	4.63 $\pm$ 0.66
Hypophosphatemic	88	6.25-15.32	10.35 $\pm$ 2.03	17-46	32.21 $\pm$ 5.49	1.5-3.5	2.95 $\pm$ 0.53
Hyperphosphatemic	21	7.05-15.16	10.80 $\pm$ 1.98	24-47	33.76 $\pm$ 5.62	6.1-9.4	7.08 $\pm$ 1.02

TABLE IV
COMPARISON OF HEMOGLOBIN, HEMATOCRIT AND SERUM PHOSPHORUS LEVELS
BETWEEN THE THREE AGE GROUPS OF RICKETS AND CONTROLS

Age in			Hemoglobin level (gm/dl)		Hematocrit value (%)		Serum phosphorus (mg/dl)	
months	Number		Range	Mean (S.D.)	Range	Mean (S.D.)	Range	Mean (S.D.)
0-3	Rickets	26	8.50-14.00	10.50±1.66	25-44	32.92±5.10	2.0-9.4	4.87±1.80
	Controls	32	6.75-14.07	10.72±1.99	21-44	32.18±5.81	2.2-9.2	4.79±1.44
4-6	Rickets	67	4.55-15.32	10.86±2.09	17-47	33.07±5.57	1.9-8.2	3.98±1.31
	Controls	33	6.00-14.87	10.71±2.33	19-44	32.42±6.40	2.1-9.0	4.68±1.36
7-24	Rickets	107	5.96-14.87	10.00±1.94	19-44	31.93±5.62	1.5-9	4.037±1.38
	Controls	35	6.00-13.26	10.22±1.99	19-41	31.40±6.14	2.1-7.5	4.34±1.33

TABLE V
COMPARISON OF SERUM CALCIUM, PHOSPHORUS AND ALKALINE PHOSPHATASE LEVELS
BETWEEN RICKETS AND CONTROLS

	Calcium (mg/dl)	Phosphorus (mg/dl)	Alkaline Phosphatase (B.U.)
Rickets	8.128 ± 1.763 (2.8-11.2)*	4.15 ± 1.44 (1.5-9.4)	14.072 ± 8.277 (2.6-37)
Controls	8.402 ± 1.495 (4.1-10.9)	4.56 ± 1.38 (2.1-9.2)	9.669 ± 5.922 (2.3-27)
P	> 0.05	< 0.05	< 0.001

* Number in parenthesis indicates the range.

Although serum alkaline phosphatase levels were significantly higher in the study group ($P < 0.001$) Ca values were not found significantly different between groups (Table V). Since the serum Ca levels were low in both groups the prevalence of hypocalcemia ($< 8 \text{ mg/dl}$) was looked for and found to be 38 % and 33 % in two groups, respectively.

Discussion

Rachitic children generally come from low socio-economic families. In these children, in addition to rickets, other nutritional deficiencies are more frequently expected. Iron deficiency anemia is the more prevalent anemia, especially in infancy. Therefore it is not surprising that 59 % of the rachitics and 55 % of the control children were suffering from anemia. Since marked hypochromia was observed in the peripheral smear of these children, it is most likely that the majority of the anemic children, if not all, had had iron deficiency anemia.

There are some cases of rickets with anemia in whom myelofibrosis has been shown.^{10, 12, 18} Myelofibrosis due to renal rickets has also been reported.¹⁹ Red cell survival in these cases showed decreased erythrocyte survival.¹⁰ In this study the mean Hb and Hct values indicated anemia in the same range of Salimpour's rickets cases.⁶ But these values were not significantly different from the control values. Control group children were especially chosen from those babies who had the same ailments of the study group, excepting rickets. It might then be concluded that in vitamin D deficiency rickets cases, anemia is most likely associated with poor diet and low socio-cultural conditions. The prevalence of very high malnutrition among these children (85 %) supports this conclusion.

In spite of low serum P levels, Hb and Hct values were not found elevated in patients with rickets. These results do not seem to support the studies of Card and Brain¹³ who found correlation between Hb concentration and the levels of serum P, in the range of the study group. Card and Brain postulated that higher serum P levels in childhood lead to a rise of erythrocyte ATP and^{2, 3} DPG which decreases oxygen affinity of Hb, may thus account for the physiologic "anemia" of childhood.

Hypocalcemia of these children may be related to the stage of the rickets, but it was also observed in the control children. So malnutrition might be a major factor for this finding. Serum and tissue alkaline phosphatase changes have often been studied in rickets.^{4, 5, 20} Although serum alkaline phosphatase values were significantly higher in the study

group (Table V), for individual values they would not serve as a differentiating factor in the malnourished, as was previously indicated.^{6,12}

Summary

Hemoglobin and hematocrit values of 200 children with vitamin D deficiency rickets under 24 months of age were compared with the values of 100 children within the same age range who had the same ailments as the study group, but no differences could be found. The diagnosis of rickets was made radiologically. Although the study group patients had statistically low serum P levels, their Hb and Hct values did not differ either from the control children's values or the study group with normal or elevated P values.

59 % of the patients with rickets had anemia (Hb < 11 gr/dl) and 55 % of the children in the control group were also anemic. It is therefore concluded that with the exclusion of very unusual cases of myelofibrosis, anemia is not a related finding of rickets.

REFERENCES

1. Fraser, D., Kooh, S. W., and Scriver, C. R.: Hyperparathyroidism as the cause of hyperaminoaciduria and phosphaturia in human vitamin-D deficiency. *Ped. Research*, 1: 425, 1967.
2. Preece, M. A., Ford, J. A. et al.: Vitamin D-deficiency among Asian migrants to Britain, *Lancet*. 1: 907, 1973.
3. Doxiadis, S. A., and Lapatsanis, P.: Infantile rickets persists in Greece. *Lancet*, 1: 1149, 1968.
4. Ozsoylu, S.: Leukocyte alkaline phosphatase activity in Rickets due to vitamin D-deficiency. *New Eng. J. Med.* 230: 1121, 1969.
5. Ozsoylu, S., and Turhan, O.: Alkaline phosphatase activity of duodenal juice in rickets due to vitamin D-deficiency. *Acta Paediat. Scandinavica*. 60: 338, 1971.
6. Salimpour, R.: Rickets in Tehran: Study of 200 cases, *Arch. Dis. Child.* 50: 63, 1975.
7. Doxiadis, S., Angelis, C., Karatzas, P., Vrottos, C., and Lapatsanis, P., Genetic aspects of nutritional rickets. *Arch. Dis. Child.* 51: 83, 1976.
8. Pena, J., Cerquero, M., Belmonte, V., del Rio, R., and Nestal, A.: Estudiosn hematologicos en el raquitismo comun. *Revista Espanola de Pediatria*. 20: 15, 1964.
9. Kagaya, H.: Haematological study on bone marrow in infancy and childhood. *Acta. Paediat. Jap.* 66: 332, 1962.
10. Orsini, A., Bernard, R., Glorieux, F., Oddo, and Panlin, R.: Resultats des epreuves an radiochrome dans les anemies du rachitisme, *Marseille Medical*, 102: 7, 1965.
11. Willemin-Clog, L., Cavaroc, M., de Laquillaumie, B., Raymaud, E. J. et Malpeuch, G.: Etude par ponctions-biopsies osseuses de l'anemie du rachitisme. *Pediatric*, 23: 5, 1968.

12. Cavaroc, M., de Laguillaumie, B., Malpeuch, G., et Raymaud, E. J.: Substractum anatomique de l'anemie du rachitisme. *Annales d'Anatomic Pathologique*. 15: 265, 1972.
13. Card, R. T., and Brain, N. C.: The "Anemia" of childhood, evidence for a physiologic response to hyperphosphatemia. *New Eng. J. Med.* 288: 388, 1973.
14. Clark, and Collip method: Originally described by Kessler, G., and Wolfman, M. *Clin. Chem.* 10: 686, 1964.
15. Fishe, C. H., and Subborow, Y.: The colorimetric determination of phosphorus. *J. Biol. Chemistry*. 66: 375, 1925.
16. Bodansky, A.: Phosphatase studies determination. *J. Biol. Chemistry*. 101: 93, 1933.
17. Nutritional anemias; report of a WHO Scientific Group, World Health Organization technical report series. 1968, pp. 405.
18. Say, B., and Berkel, I.: Idiopathic myelofibrosis in an infant. *J. Ped.* 64: 580, 1964.
19. Schlackman, M., Green, A. A. and Naiman, J. L.: Myelofibrosis in children with chronic renal insufficiency. *J. Ped.* 87: 720, 1975.
20. Özsoylu, Ş., and Kanra, G.: Tissue alkaline phosphatase activity in rickets due to vitamin D deficiency. *Turkish J. of Ped.* 16: 53, 1974.
21. Reddy, V., and Srikantia, S. G.: Serum alkaline phosphatase in malnutrition children with rickets. *J. Ped.* 71: 595, 1967.