Rickets in black children beyond infancy in Natal

R. Bhimma, J. M. Pettifor, H. M. Coovadia, M. Moodley, M. Adhikari

Objective. To determine the clinical spectrum of rickets among black children admitted to King Edward VIII Hospital, Durban.

Design. Prospective study of black children with rickets beyond infancy.

Setting. Hospital-based population; King Edward VIII Hospital, Durban.

Participants. A total of 37 patients, aged 1 - 12 years, were recruited over a 3-year period. None had been on vitamin D or calcium supplementation prior to investigation.

Outcome measures. Rickets was diagnosed clinically, radiologically and biochemically (by a raised alkaline phosphatase value of > 350 IU). Gastro-intestinal, hepatic and renal glomerular causes were excluded in all patients using standard clinical and laboratory criteria.

Results. Twenty-three patients were diagnosed as having privational rickets. Nine had 25-hydroxyvitamin D (25-OHD) levels of < 10 ng/ml while 14 had levels within the normal range and were suspected of having dietary calcium deficiency. Ten had a phosphopenic variety of rickets; the remaining 4 had healing or healed rickets on the basis of radiological assessment and normal biochemical values. Pain together with difficulty in walking and bowing of the lower limbs were the main reasons for presentation. The main clinical findings were thickened wrists and ankles and rickety rosary (100%), stunting (85%), anterior bowing of lower limbs (70%) and genu valgum (65%). The calcium and vitamin D deficiency group showed a much better clinical, biochemical and radiological response to therapy than the phosphopenic group on follow-up (18 patients).

Conclusion. This is the first substantial report on rickets in the older child in Natal, which extends the findings from Transvaal, thereby establishing a recognisable pattern of rickets beyond infancy in South Africa. It draws attention to the common clinical presentations which may alert health professionals to the presence of this problem. This report demonstrates that the two commonest types are privational rickets (due to calcium and/or vitamin D deficiency) and phosphopenic rickets.

S Afr Med J 1995; **85:** 668-672.

Department of Paediatrics and Child Health, University of Natal, and MRC Mineral Metabolism Research Unit, Department of Paediatrics, University of the Witwatersrand

R. Bhimma, D.C.H. (S.A.), M.MED., F.C.P. (S.A.)

J. M. Pettifor, M.B. B.CH., F.C.P. (S.A.), PH.D.

H. M. Coovadia, M.D., F.C.P. (S.A.), M.SC. (IMM.)

M. Moodley, M.B. CH.B., F.C.P. (S.A.), M.R.C.P.

M. Adhikari, F.C.P. (S.A.), M.D.

Rickets along with many other nutritional deficiency diseases remains prevalent in many developing countries. Moreover, severe cases, which are no longer encountered in industrialised nations, have recently been reported from these areas.[1] In most industrialised countries rachitic lesions are generally no longer due to vitamin D deficiency,[2] although in Britain nutritional rickets remains a problem in the Asian community. In the USA, vitamin D deficiency rickets has become a rare disease; however, recently attention has been drawn to its occurrence in infants of vegetarian and black mothers. Outside the infant age group, hypophosphataemic vitamin D-resistant rickets is the commonest form in a number of developed countries.

We have a far better understanding of the aetiology, pathogenesis and treatment of the various forms of rickets and osteomalacia seen in children because of recent advances in vitamin D metabolism.[3] Reversible rickets beyond infancy is of particular interest as vitamin D deficiency is likely to be less prevalent in tropical and subtropical regions (such as Natal) where there is an abundance of sunshine throughout the year.

In 1962 Taitz[4] described rickets in black children over the age of 2 years from the Eastern Transvaal. Although some of these cases had identifiable defects such as hypophosphataemic vitamin D-resistant rickets, the majority could not be ascribed to any specific aetiology. More detailed studies undertaken by Pettifor *et al.*[5] revealed that these patients had a calcium deficiency type of rickets related to low dietary calcium intake.

In Natal rickets remains the commonest metabolic bone disorder seen in children; however, the causes and clinical spectrum of the disease have not been delineated adequately. We therefore undertook an investigation of patients admitted to King Edward VIII Hospital with rickets beyond infancy in a prospective study which commenced in 1991.

Patients

Thirty-seven patients, with ages ranging from 1 to 12 years, who were diagnosed as having rickets and were admitted over a 3-year period to the King Edward VIII Hospital, Durban, are the subjects of this study.

The diagnosis of rickets was made on the basis of clinical and radiological features suggestive of this disease together with a raised serum alkaline phosphatase level (> 350 IU/l). Vitamin D deficiency rickets was diagnosed on the basis of low serum 25-hydroxyvitamin D (25-OHD) concentrations (< 10 ng/ml) in association with other biochemical features of calciopenic rickets (low serum calcium and elevated alkaline phosphatase values). Dietary calcium deficiency was considered the diagnosis in children who had evidence of calciopenic rickets, but in whom normal 25-OHD concentrations were found.[5] Phosphopenic rickets, including

X-linked hypophosphataemic vitamin D-resistant rickets and other renal tubular defects, were diagnosed if serum calcium and 25-OHD values were normal but serum phosphate concentrations were low. Although serum parathyroid hormone concentrations were measured, the results are not included as the values obtained appeared to be unreliable. Healing rickets was diagnosed radiologically by the presence of a well-demarcated zone of provisional calcification at the growth plate, while healed rickets was considered a possible diagnosis in those patients who had bone deformities suggestive of rickets, but in whom serum biochemical values was normal and no radiological evidence of active rickets was noted on wrist radiographs.

Methods

Routine biochemical investigations were performed on all children; in addition serum for 25-OHD and 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D) levels was taken at the time of admission. This was stored at –20°C and assayed in batches in the MRC Mineral Metabolism Research Unit, Johannesburg. 25-OHD and 1,25-$(OH)_2$D were measured by competitive binding assay[6] and radioreceptor assay[7] respectively. Gastro-intestinal, hepatic and renal glomerular causes were excluded by standard criteria. Dietary intake was assessed by a history taken from the parent or guardian.

Results

On the basis of biochemical and radiological findings, the patients were divided into three major categories: (*i*) privational rickets due to vitamin D and/or calcium deficiency (23 patients); (*ii*) phosphopenic rickets (10 patients); and (*iii*) healing or healed rickets (4 patients).

The main mode of presentation in our patients was difficulty in walking together with lower limb deformities. Only 1 child had bronchopneumonia as the presenting complaint. In addition, most patients with privational rickets had muscle pain. However, obvious muscle weakness was not present except in those patients suspected of having an acquired form of phosphopenic rickets. Dietary assessment based on a detailed history taken from the parent or guardian revealed that all patients had a diet consisting mainly of maize with a variety of vegetables and occasionally meat, with very little intake of milk and other dairy products. Vitamin and mineral supplementation, which is a common practice in more affluent communities, was completely absent in these patients. However, none of the children had overt evidence of protein energy malnutrition. Although 85% of the patients showed stunting, weight was less severely affected, particularly in the younger children. All patients on clinical examination were found to have rickety rosary and thickened wrists and ankles. Kyphoscoliosis was present in only 46% of all subjects. Although hypotonia was a frequent finding (78%) in the vitamin D deficiency group, none exhibited the complications of recurrent chest infections (Table I). Sixteen of the 23 patients with privational rickets were of rural origin.

Patients with low serum 25-OHD levels had significantly lower serum phosphate, 25-OHD and 1,25 $(OH)_2$D levels (Wilcoxon 2-sample test, $P < 0,05$) than those in the calcium deficiency group. There were no statistically significant differences with regard to age, serum calcium or alkaline phosphatase levels between the two groups. Combining the results from the vitamin D-deficient and dietary calcium deficiency groups, there was a positive correlation between serum 25-OHD and 1,25 $(OH)_2$D values ($r = 0,486$, $P = 0,025$) (Tables II and III).

Table I. Clinical findings on presentation

Clinical findings	Vitamin D deficiency	Calcium deficiency	Hypophos-phataemic rickets	Healed rickets
Total	9	14	10	4
Bossing	6	5	4	3
Thickened wrists and ankles	9	14	10	3
Rickety rosary	9	14	10	3
Harrison's sulcus	3	3	5	2
Violin-case deformity	3	1	2	0
Genu valgus	6	9	6	2
Anterior bowing of lower limbs	7	8	8	3
Windswept deformity	2	1	0	0
Scoliosis	2	2	3	0
Kyphosis	0	0	3	1
Lordosis	2	7	6	2
Dental caries	3	1	3	0
Hypotonia	6	3	0	0
Bronchopneumonia	0	0	2	0
Muscle weakness	0	0	2	0
Stunting	6	11	10	3

Table II. Vitamin D deficiency

Patient	Age	Sex	U/R	Alk phos (IU/l)	Ca^{2+} (mmol/l)	PO_4^{2-} (mmol/l)	25-OHD (ng/l)	1,25-$(OH)_2$D (pg/ml)
1	3	F	U	2 040	2,01	1,00		
2	3	F	R	432	2,33	1,40	2,1	57
3	5	M	R	1 040	2,27	0,46	6,6	57
4	2	M	R	893	1,78	1,07	6,5	58
5	10	M	R	1 082	1,95	1,55	7,8	89
6	2	F	R	810	2,06	1,32	< 4,0	47
7	6	M	R	2 465	1,71	1,29	< 3,0	67
8	12	F	R	593	2,54	0,60	< 4,0	45
9	12	F		2 754	2,15	0,99	6,2	101
Mean	6,1			1 512	2,09	1,08	3,7	58
SD	4,2			934	0,27	0,36	3,5	31
Reference values				< 350	2,25 - 2,75	1,3 - 1,8	12 - 40	20 - 50

U = urban; R = rural; PO_4^{2-} = phosphate.
Ca^{2+} = total serum calcium.

Table III. Calcium deficiency rickets

Patient	Age	Sex	U/R	Alk phos (IU/l)	Ca^{2+} (mmol/l)	PO_4^{2-} (mmol/l)	25-OHD (ng/l)	1,25-$(OH)_2$D (pg/ml)
1	3	M	U	486	2,45	2,12	25,8	94
2	7	M	U	733	2,20	1,78	22,5	109
3	12	M	R	648	2,38	2,29	17,5	222
4	4	F	R	923	2,22	0,68	16,1	84
5	11	M	R	431	2,03	1,83	18,4	116
6	12	M	R	623	1,61	1,80	11,6	185
7	10	M	R	989	1,70	1,27	12,6	117
8	5	F	R	689	2,39	2,20	16,2	121
9	2	M	R	606	2,27	1,29	17,2	79
10	1	M	R	1 005	1,94	1,20	20,5	52
11	5	F	R	594	2,21	1,51	22,7	139
12	4	F	R	689	2,32	1,60	15,8	163
13	6	M	R	1 087	2,10	1,56	20,1	151
14	8	F	R	635	2,52	1,13		
Mean	6,4			724	2,16	1,58	18,2	125
SD	3,7			200	0,28	0,45	4,0	46

In the phosphopenic group all 10 patients were of rural origin with dietary intake similar to that of patients with privational rickets. Eight of these patients had clinical, biochemical and radiological features in keeping with the familial variety of vitamin D-resistant rickets (diagnosed on the basis of absence of muscle weakness and osteopenia on radiographs), 1 had Fanconi syndrome and 1 had an acquired type of hypophosphataemic rickets. All had normal serum calcium and 25-OHD levels (Table IV). Muscle weakness was a prominent finding in the 2 patients who did not have the familial variety of hypophosphataemic vitamin D-resistant rickets.

Table IV. Hypophosphataemic rickets

Patient	Age	Sex	U/R	Alk phos (IU/l)	Ca^{2+} (mmol/l)	PO_4^{2-} (mmol/l)	25-OHD (ng/l)	1,25-$(OH)_2$D (pg/ml)
1	3	M	R	552	2,33	0,78	24,8	64
2*	1	M	R	658	2,32	0,99	28,2	29
3	8	F	R	1 204	2,27	0,77	14,3	85
4	4	F	R	522	2,34	0,03	22,5	70
5†	8	F	R	974	2,39	0,65	18,8	<10
6	8	F	R	358	2,67	0,63	17,2	14
7	6	F	R	471	2,40	0,44		
8	4	F	R	453	2,27	0,83	23,4	23
9	8	F	R	353	2,85	0,86	14,7	20
10	2	F	R	695	2,75	0,34	25,2	40
Mean	5,3			604	2,44	0,72	21,0	39
SD	2,9			298	0,18	0,21	4,9	29

* Renal tubular acidosis.
† Probable acquired hypophosphataemic rickets.

In the patients with healing or healed rickets biochemical values were normal except for a mildly elevated alkaline phosphatase level. No features of active rickets were noted on radiological assessment (Table V).

Table V. Healing or healed rickets

Patient	Age	Sex	U/R	Alk phos (IU/l)	Ca^{2+} (mmol/l)	PO_4^{2-} (mmol/l)	25-OHD (ng/l)	1,25-$(OH)_2$D (pg/ml)
1	4	M	U	378	2,46	2,23	22,7	110
2	4	M	R	494	2,51	1,38	27,3	106
3	3	F	R	724	2,33	2,17	24	23
4	3	M	R	357	2,49	1,58		
Mean	3,5			463	2,45	1,84	24,7	81
SD	0,6			199	0,08	0,42	2,4	50

Treatment

The majority of patients with privational rickets were treated with a combination of vitamin D (cholecalciferol) 5 000 - 10 000 IU/d and calcium supplements (Calcium-Sandoz) 500 - 1 000 mg/d, while those with the phosphopenic variety of rickets were given alfacalcidiol (One Alpha) 0,5 - 1 µg twice a day, phosphate supplements (Phosphate-Sandoz) 2 - 2,5 g/d and a thiazide diuretic (Diazide) 1/2 tablet daily. The one patient diagnosed as having renal tubular acidosis had Shohl's solution 20 ml 4 times a day added to his treatment regimen for correction of acidosis.

Follow-up

Eighteen patients reported for follow-up. After commencement of therapy patients were assessed at 6 weeks and then at 3-monthly intervals for evidence of healing. This was done using clinical, radiological and biochemical criteria. Clinical criteria for healing were defined as improvement in pain, tone, deformities, mobility and growth; biochemical assessment included normalisation of serum calcium and phosphate levels with a decrease in alkaline phosphatase, and radiological improvement was defined as improved bone density, and reappearance of the zone of provisional calcification.

Twelve patients with privational rickets on follow-up showed a much better clinical response to therapy than those in the phosphopenic group, with improvement of pain and tone within 4 - 6 weeks of commencing therapy. The bony deformities remained persistent but no surgical intervention was undertaken at this stage. The patients with privational rickets also showed marked improvement on follow-up radiological and biochemical assessment.

The 5 patients with phosphopenic rickets reporting for follow-up showed amelioration of symptoms with improved biochemistry, although deformities and diminished mobility remained unchanged. After therapy for a year, with improved biochemical values, 4 patients were subjected to corrective osteotomies. None showed complications of hypercalcaemia or nephrocalcinosis on follow-up and therapy was continued.

Discussion

Privational rickets emerges as the commonest variety seen in older children, comprising 62% of patients in our study. It

encompasses a spectrum of disorders ranging from pure dietary calcium deficiency to one of pure vitamin D deficiency, most cases resulting from an interplay of both factors. Despite an abundance of sunshine, vitamin D deficiency, diagnosed by low circulating levels of 25-OHD, was found in 9 of the 37 patients. These children could not be differentiated on age, dietary patterns or clinical presentation from those children presenting with presumed dietary calcium deficiency, diagnosed by normal circulating levels of 25-OHD with low or low-normal calcium levels. Dietary habits and serum calcium levels in these children were similar to those found in other studies done in the Eastern Transvaal by Pettifor *et al.*[8] The diet of rural South African children is simple, consisting of the staple maize meal, cooked to a thick porridge, plus a stew of vegetables in season, meat when available, with little or no milk and other dairy products.[8] Although quantitative analysis of dietary calcium in our patients had not been undertaken, it would appear that the calcium intake of children in our study would be well below the recommended dietary allowance of 800 - 1 200 mg/d set by the National Academy of Science.[9] It is generally considered that a low dietary calcium intake is of little clinical significance, with very little evidence being available to incriminate its role in the production of rickets or osteomalacia.[10] However, studies done by Pettifor *et al.*[5] have shown that dietary calcium deficiency, if continued for long enough and if severe enough, may progress to clinical and radiological rickets.

In the group of patients diagnosed as having vitamin D deficiency, high phytate- or phosphorus-containing diets could have stimulated an increase in parathyroid hormone secretion and 1,25-$(OH)_2D$, probably through the impairment of intestinal calcium absorption.[11] Elevation of 1,25-$(OH)_2D$ levels increase the catabolism and shorten the half-life of 25-OHD, thus increasing vitamin D requirements.[12] Thus it is apparent that dietary calcium content and its availability in the intestine for absorption play important roles in precipitating vitamin D deficiency, especially in those individuals whose vitamin D supply is marginal. Also, changes in calcium balance induced by the high-fibre diet may indirectly affect vitamin D metabolism.[13] Although vitamin D deficiency is likely to be the main pathogenetic mechanism, coexisting calcium deficiency is probably a further contributory factor. Vitamin D deficiency in developed countries is almost totally confined to the socio-economically disadvantaged, the elderly, vegans, and members of certain religious groups, who either do not get sufficient sunlight because of dress or who abstain from the intake of milk or milk products. All our patients come from a socio-economically disadvantaged community, the majority are from rural areas, and despite urbanisation of a few, dietary habits remain largely unchanged with intake of vitamin D-fortified foods and dairy products being suboptimal. The exclusion of direct sunlight, for example in ethnic groups who wear dark veils and thick garments when outdoors or who are confined to their homes most of the time, predisposes to vitamin D deficiency through a lack of vitamin D formation in the skin. In Natal the dress of the rural black child allows sufficient skin exposure, with basking in the sun being a common pastime among rural black children. Thus it is surprising that older children are presenting with low serum 25-OHD levels. It is possible that the recent drought, together with the social unrest, had aggravated the poor calcium intake in these children, resulting in the development of rickets. It is possible that the bony deformities, together with pain, would have resulted in these children being confined indoors for longer periods, thus predisposing to the development of vitamin D deficiency rickets. Black children, however, do require greater exposure to sunlight to prevent rickets, because their skin pigmentation reduces the penetration of sunlight.[14] Hahn and Avioli[15] have demonstrated lower levels of 25-OHD in blacks and other studies have shown that melanin reduces the amount of previtamin D_3 produced in human skin in response to simulated sunlight.[16] However, dark skin is not an absolute inhibitor of vitamin D synthesis, as black subjects exposed to proportionately larger doses of UV radiation produce similar amounts of vitamin D.[17]

In industrialised countries air pollution results in a thick industrial fog consisting of chemical products generically known as anthropogenic aerosols. The actinic radiation is subject to greater scattering and to more intense absorption by the ozone layers of the stratosphere and is therefore insufficient for cholecalciferol synthesis. In Natal, air pollution and lack of sunlight exposure are not major problems and are unlikely to be responsible for vitamin D deficiency except in institutionalised or very young children.

Thus in the South African situation, a diet low in calcium with a high phytate and oxalate content, limited intake of milk or other dairy products, lesser periods of exposure to sunlight and cutaneous pigmentation operate via a variety of mechanisms, either singly or in combination, to predispose to the development of rickets.

The other major category of rickets seen in our patients is the phosphopenic variety. Dietary lack of phosphate and intestinal binding were excluded on history. Dietary deficiency of phosphate occurs only in exceptional circumstances as phosphate is ubiquitous in all foods. All patients showed the typical biochemistry of phosphopenic rickets with hypophosphataemia, normocalcaemia and elevated alkaline phosphatase values. Vitamin D assays showed normal 25-OHD and normal to slightly elevated 1,25-$(OH)_2D$.[17] Of the 8 patients diagnosed as having familial X-linked hypophosphataemic vitamin D-resistant rickets, none had a positive family history of rickets. Biochemical and radiological assessments of the parents were undertaken in only 3 of these patients as the parents of the other children were not available for testing. None of the parents showed any clinical, radiological or biochemical stigmata of having had rickets or osteomalacia. The absence of a family history is not surprising as it has been well documented that approximately 30% of cases appear to be the result of sporadic mutations.[18]

Conclusion

This study highlights the likely causes and clinical spectrum of rickets in black children in Natal; the majority of children have privational rickets and are mainly of rural origin. The diagnosis is usually not difficult to make clinically, and can easily be supported by simple biochemical and radiological investigations. In patients with less obvious clinical features of the disease the findings of osteopenia and an elevated

alkaline phosphatase level should alert the physician to the possibility of rickets. These findings lay the foundation for more extensive and detailed studies to assess the feasibility of dietary manipulation and food fortification in rural black children.

We thank Ms D. Zacken for the excellent technical assistance rendered with regard to vitamin D assays, the Department of Chemical Pathology, University of Natal, Durban, for doing the parathyroid hormone levels, Mrs M. Singh for her help in data collection and collation, and the paediatric medical and nursing staff in their assistance in patient management. We also wish to thank the superintendent of King Edward VIII Hospital for permission to publish.

REFERENCES

1. Jain L, Chaturvedi SK, Saxena S, Udawat M. Atrophic rickets: a pattern to be reckoned with in tropical countries. *J Trop Pediatr* 1985; **31:** 167-169.
2. Barness LA. Nutrition and nutritional disorders. In: Behrman RE, Kliegman RM, Nelson WE, Vaughan III VC, eds. *Nelson's Textbook of Pediatrics.* Philadelphia: WB Saunders, 1987: 133-154.
3. Pettifor JM. Recent advances in paediatric metabolic bone disease: the consequences of altered phosphate homeostasis in renal insufficiency and hypophosphataemic vitamin D-resistant rickets. *Bone Miner* 1990; **9:** 199-214.
4. Taitz LS. The role of the parathyroid gland in vitamin D deficiency rickets. MD thesis, University of the Witwatersrand, 1962: 132.
5. Pettifor JM, Ross P, Wang J, Moodley G, Couper-Smith J. Rickets in children of rural origin in South Africa: is low dietary calcium a factor? *J Pediatr* 1978; **92:** 320-324.
6. Haddad F, Chyu K. Competitive protein-binding radioassay for 25-hydroxycholecalciferol. *J Clin Endocrinol Metab* 1971; **33:** 992-995.
7. Reinhardt TA, Horst RL, Orf JW, Hollis BW. A microassay for 1,25-dihydroxyvitamin D not requiring high performance liquid chromatography: application to clinical studies. *J Clin Endocrinol Metab* 1984; **58:** 91-98.
8. Pettifor JM, Ross P, Moodley G, Shuenyane E. Calcium deficiency in rural black children in South Africa — a comparison between rural and urban communities. *Am J Clin Nutr* 1979; **32:** 2477-2483.
9. Pettifor JM. Dietary calcium deficiency. In: Glorieux FH, ed. *Rickets* (Nestle Nutrition Workshop Series No. 21). New York: Raven Press, 1991: 122-142.
10. Walker ARP. The human requirement of calcium: should low intakes be supplemented? *Am J Clin Nutr* 1972; **25:** 518.
11. Calvo MS, Kumar R, Heath H. Elevated secretion and action of serum parathyroid hormone in young adults consuming high phosphorus, low calcium diets assembled from common foods. *J Clin Endocrinol Metab* 1988; **66:** 823-829.
12. Clements MR, Johnson L, Fraser DR. A new mechanism for induced vitamin D deficiency in calcium deprivation. *Nature* 1987; **325:** 62-65.
13. Batchelor AJ, Compston JE. Reduced plasma half-life or radio-labelled 25-hydroxyvitamin D_3 in subjects receiving a high-fibre diet. *Br J Nutr* 1983; **49:** 213-216.
14. Matthews SJ, Versfeld GA. Rickets in cerebral palsied children: a report of two cases. *J Pediatr Orthop* 1986; **6:** 717-720.
15. Hahn TH, Avioli LV. Anti-convulsant osteomalacia. *Arch Intern Med* 1975; **135:** 997-1000.
16. Pettifor JM, Ross FP, Quirk M, Moodley GP, Cavaleros M. Acquired hypophosphataemic vitamin D resistant rickets in black children. *Bone Miner* 1986; **1:** 307-319.
17. Clifford WL, Paris PW, Holick MF. Indian and Pakistani immigrants have the same capacity of Caucasians to produce vitamin D in response to ultraviolet irradiation. *Am J Clin Nutr* 1986; **44:** 683-685.
18. Pettifor JM. Metabolic bone disorders. In: Coovadia HM, Loening WEK, eds. *Paediatrics and Child Health.* 3rd ed. Cape Town: Oxford University Press, 1992: 455-467.

Accepted 14 Sep 1994.