STUDIES IN RICKETS IN THE CAPE PENINSULA

I. CRANIAL SOFTENING IN A COLOURED* POPULATION AND ITS RELATIONSHIP TO THE RADIOLOGICAL AND BIOCHEMICAL CHANGES OF RICKETS

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Rickets still occurs frequently in tropical and sub-tropical countries. There have been recent reports from Israel,[1] the Phillipines,[2] Nigeria,[3] Singapore,[4] and South Africa.[5,6] Feldman in 1950 noticed that rickets was common in Johannesburg, although he did not assess its incidence. He thought that the urbanized Native infant was not sufficiently exposed to sunlight.[6] On the other hand, Kark and le Riche, in a survey of Native school children, found it to be uncommon in the rural areas.[7]

In any survey of rickets the diagnosis of the early case presents a problem. Histological abnormality at the costo-chondral junction is probably the earliest sign of rickets, but without this evidence cases must be assessed by clinical, radiological, and biochemical changes.

Radiological changes probably occur only when rickets is fairly advanced. Craniotabes is sometimes cited as the earliest clinical sign of rickets,[8,9] but below the age of 3 months this phenomenon can occur in normal children.[10] Even over this age, some authorities have regarded it as a normal physiological variant.[11]

Routine biochemical tests in the investigation of rickets include serum levels of alkaline phosphatase, inorganic phosphorus, and calcium. Abnormal phosphatase levels have been found to be a reliable index of early activity, preceding radiological changes, and more constant than reduced serum inorganic phosphorus.[13,14]

Objects of this Investigation

1. To determine the incidence of rickets in a hospital population of urbanized Coloured out-patients.

2. To assess the frequency and significance of craniotabes between the ages of 3 months and 1 year.

3. To investigate the value of altered serum levels of alkaline phosphatase, phosphorus, and calcium in diagnosing early rickets and in assessing progress.

* Coloured signifies people originating from 4 principal stocks: Hottentot, Bushman, European and, more recently, Bantu. Ten of these subjects were pure Bantu.

METHODS

All children between the ages of 3 months and 1 year attending at Paediatric Out-patient Department at Groote Schuur Hospital during the month of October 1959 (105 in all) were examined for clinical signs of rickets. Special attention was directed to the presence of cranial softening and its severity as detected by palpation. Cranial softening was not considered to be present unless it involved an area about 1 inch in diameter. It was graded as mild when only a small area of the occipital bone was involved — occasionally unilaterally. If the softening was more extensive and indented with only slight pressure, it was classified as severe.

Children aged 3 - 12 months (selected at random) with cranial softening, who were found during the months of September and October, were further investigated for other evidence of rickets. Radiographs of the wrist were obtained in all these cases and, in many, chest films. The X-ray films were examined by at least 4 observers (3 of whom saw all the films†) and were classified as showing advanced rickets, early rickets, or no rickets. There were some cases in which it was difficult to be certain if rickets was present in its earliest stage, and these were appropriately classified as 'dubious'. A control group of Coloured children between 3 and 12 months of age, without cranial softening, were also X-rayed to assess the incidence of rickets. Serum-alkaline phosphatase, inorganic phosphorus, and calcium levels were determined. Most patients were seen again 4 - 8 weeks later when radiographs and biochemical tests were repeated. Of 23 children who had rickets and were seen subsequently, 8 received calciferol (ostelin forte,‡ 1 c.c. intramuscularly, i.e. 600,000 units of vitamin D_2) and the remainder were not treated.

† Dr. L. Werbeloff and the authors of this article.

‡ Supplied by Messrs. Glaxo-Allenburys (S.A.) (Pty.) Ltd.

RESULTS

1. *Total Incidence of Cranial Softening Seen During One Month*

A total of 105 patients between 3 months and 1 year of age were reviewed (Fig. 1), 49 of whom had cranial softening. They were divided into 2 groups according to age — children of 3 - 6 months, inclusive, in group 1, and

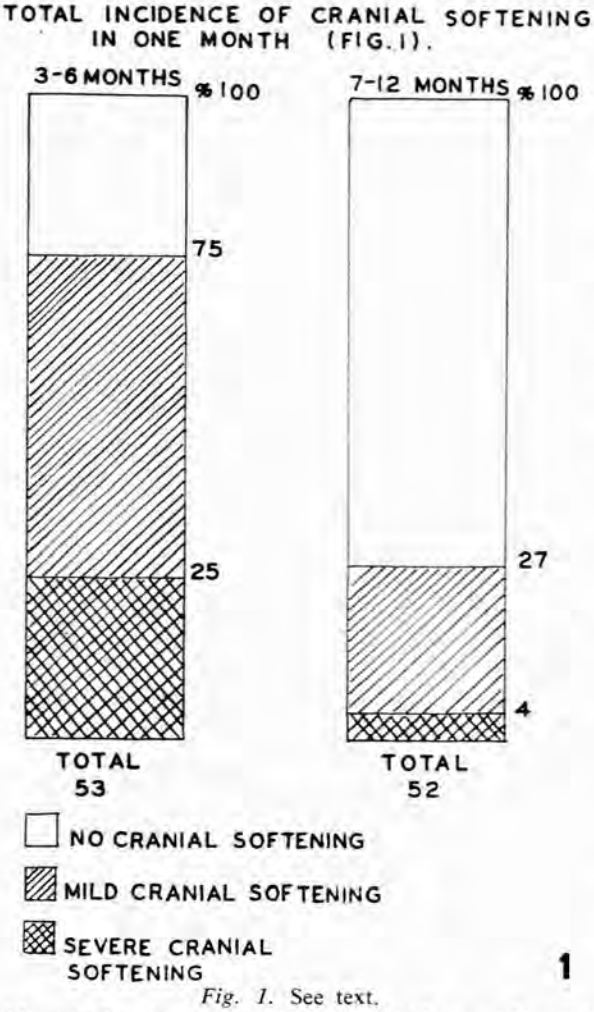

Fig. 1. See text.

7 - 12 months in group 2. The incidence of cranial softening was higher in group 1 (75%) compared to group 2 (27%). There was also a higher incidence of severe cranial softening in the younger age group (25%, compared to 4% in group 2).

2. *Significance of Cranial Softening*

In group 1 over 40% of cases with cranial softening (14 out of 34) had definite radiological evidence of rickets. In group 2 the incidence of rickets in cases with cranial softening was higher (over 60% — 13 out of 21). This difference is not statistically significant (P ·1). Cases with severe cranial softening were no more liable to rickets than those with mild cranial softening (Table I).

In a control group of subjects without cranial softening, 13 were between 3 - 6 months of age, and 14 between 7 - 12 months. None of the younger group had rickets, but 5 of the older group had radiological rickets.

TABLE I. COMPARISON OF CASES WITH SEVERE AND MILD CRANIAL SOFTENING

	Cranial softening	*No rickets*	*Radiological rickets*		*Total*
			Mild	*Severe*	
Severe	27	16	8	3	11
Mild	28	12	7	9	16
Total	55	28	15	12	27

It is noteworthy that rickets actually appears commoner with 'mild' craniotabes than with the 'severer' grade. This is evidently related to the age incidence, since radiological rickets was commoner in the 7 - 12-month group (60% of all cases with cranial softening) than in the 3 - 6-month group (40%), while severer craniotabes was commoner at 3 - 6 months (24 cases) than at 6 - 12 months (3 cases).

BIOCHEMICAL CHANGES IN RICKETS (TABLE II)

The marked difference in mean alkaline-phosphatase levels between patients with definite rickets and those with dubious or no rickets, was significant ($P<·001$). There was no significant difference in the mean levels of those patients with dubious rickets, cranial softening with no rickets, and controls without cranial softening. The difference in the mean levels between advanced and early rickets was possibly significant ($P<·05$).

There was no difference in inorganic phosphorus levels in the patients with dubious radiological changes, controls without cranial softening, and those with cranial softening. Although the mean values fall progressively as rickets becomes more advanced, the differences between the various groups are not significant.

There was a disturbing overlap in individual cases in various groups — some patients with rickets had normal serum-alkaline phosphatase and phosphorus readings, while some without radiological abnormality had elevated levels of alkaline phosphatase.

There was no correlation between biochemical changes and the severity of cranial softening. Half the patients with radiological rickets had a serum calcium below 9 mg. per 100 ml. Two cases with early rickets had a calcium × phosphorus quotient above 40, yet neither showed any evidence of healing.

PROGRESS OF CASES

Radiological

Radiological improvement was observed (after 4 weeks) in 11 cases of rickets, 7 of whom had received calciferol and 4 not. No change was noted in 7 patients, 6 of whom had had no therapy, and the radiological appearances were worse in 5, none of whom had received treatment.

Radiological rickets did not develop in any patient with cranial softening who had normal X-ray appearances originally and who received no treatment.

In cases of originally doubtful radiological appearances definite changes developed in only 1 case. In 3 cases the changes remained doubtful, and in 4 cases, 1 of whom had received calciferol, the appearances became definitely normal.

Cranial Softening

Twenty-two cases of rickets with cranial softening were re-examined after a 4 - 8 week interval. Cranial softening was still present and had not changed in 18 of these. In some of these cases the rickets had healed radiologically. Eleven patients with cranial softening, but without

pearance it became higher in 1 and was unaltered in another.

In cases showing unchanged normal or dubious radiological appearances, most had a higher phosphorus level on the second occasion (in no instance was the serum phosphorus below 4·5 mg. per 100 ml.).

DISCUSSION

1. *Incidence of Rickets*

Approximately 50% of Coloured children between the ages of 3 and 12 months had cranial softening and in this investigation half of these (i.e. 25% of the total) had definite radiological evidence of rickets. In addition there are those children in the 7 - 12-month age group who have rickets without cranial softening. This would increase the total incidence of rickets in the 3 - 12-month group to over 30%. We have excluded all cases in which the radiological diagnosis was not definite and those cases who had slightly abnormal biochemical findings but no radiographic evidence of rickets. In fact the biochemical and radiological findings were completely normal in only 10 of the 51 cases with cranial softening.

However, both pneumonia and gastro-enteritis are commonly associated with rickets and, since these are the two commonest complaints of out-patients, it is likely that we are obtaining an exaggerated estimate of the incidence of rickets in general. It is also possible that the incidence is especially high in the spring months.

Nevertheless Follis,[15] in a survey of rickets in the USA between 1925 - 1942, observed an incidence of 63% in the first 2 years of life (based on histological changes in autopsy material). Gillman[16] found an incidence of 50% in Johannesburg in children under 1 year, based on the same criteria. Histological evidence, however, cannot really be compared with that obtained by other methods. The incidence of rickets in Great Britain, where bread was enriched with calciferol, is very low. In a recent survey only 17 out of 3,328 children had active rickets.[17] It is also uncommon in New Zealand,[18] but is common in several tropical and sub-tropical parts of the world, as remarked above.

2. *Significance of Cranial Softening*

The incidence of this sign seems to vary in different geographical areas, being a very rare feature of rickets in Nigeria[3] and Singapore,[4] but common in Cape Town among both Coloured and Bantu children.

Approximately half the cases of cranial softening had no radiological evidence of rickets. It is possible that the cranial softening in these cases was either the first indication of rickets, the only remaining sign of rickets, or a normal variant. We have not observed that rickets develops in any case of craniotabes which did not originally have radiological signs, nor was there evidence of healed rickets on the normal radiographs, so that we feel it is unlikely to be either an early or a residual manifestation of rickets in these cases. We have also seen cases of rickets healing radiologically while the cranial softening persisted, and conversely, cranial softening becoming normal before radiological healing. We feel, therefore, that approximately half the cases of cranial softening bear no relationship to rickets, and may be physiological. However, the fact that the other half was associated with radiological rickets is no proof that it, too, was not physiological, unless it is shown that rickets is not found in the *absence* of craniotabes.

In the 3 - 6-month age group we were in fact unable to detect rickets in the absence of cranial softening, so that at this age it appears that some cases of cranial softening are directly associated with rickets. In the older group there were cases of rickets with no cranial softening, although the incidence of rickets in this group was less than in those with cranial softening (approximately half). There does seem to be an increased likelihood of cranial softening being associated with rickets above 6 months than below this age (but this has not been proved statistically). Furthermore, craniotabes not associated with radiological rickets appears to behave differently in follow-up examinations. In most of these cases it improved or 'healed' completely without treatment, whereas, when associated with definite rickets, it was more likely to persist unchanged.

In conclusion, there appear to be 2 varieties of cranial softening: one completely unassociated with rickets, and possibly physiological; and the other, an identical softening which is associated with rickets and which displays a different natural history.

3. *Significance of Biochemical Changes*

Although most cases of rickets had elevated serum-alkaline phosphatase and depressed phosphorus levels, there were cases in which the serum levels were not altered, so that these parameters cannot therefore be regarded as reliable indices of activity. High alkaline-phosphatase levels were not always associated with low serum phosphorus, as was observed by Wayburne and Dean.[12] There were also cases with normal radiological appearances in which the serum levels were abnormal. There was no evidence that biochemical changes in fact preceded radiological abnormalities, as there was no difference in subsequent radiological appearances in these cases.

The cases which present the most difficult diagnostic problems are those with dubious radiological appearances, and it was hoped that biochemical changes would be of assistance in these.[13, 14] However, there was no correlation between biochemical abnormality and the future course in this group of patients, most of whom recovered in spite of having abnormal serum chemistry. One case, however, progressed to definite radiological rickets with normal serum chemistry. A change of X-ray diagnosis on follow up from 'dubious' to 'normal' presumably indicates that rickets was actually present in the 'dubious' phase.

Serial serum-alkaline phosphatase and phosphorus levels varied considerably in cases showing no radiological changes at subsequent examinations. It is of course possible that this is a true reflection of metabolic bone changes which cannot be detected radiologically, but, since we were unable to demonstrate any correlation between radiological and biochemical changes, this is unlikely, and radiology must be considered our most reliable index of diagnosis.

CONCLUSIONS

1. Appreciable degrees of cranial softening are very common (50%) in non-European children aged 3-12 months attending the out-patient department at Groote Schuur Hospital.

2. Cranial softening can certainly occur without rickets; it does not necessarily lead to rickets, does not disappear when rickets heals, and may in fact have no relation to rickets whatever.

3. Rickets is extremely common in the patients here considered, the incidence being certainly over 30% and possibly as high as 80%.

4. Radiological evidence of rickets, although probably indicative of relatively advanced rickets, is the most reliable criterion for diagnosis and of progress. We have not demonstrated that cranial softening or biochemical changes preceded radiological abnormalities.

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APPENDIX

The chemical methods used were:

Serum-alkaline phosphatase: Shinowara, G. Y., Jones, L. M. and Reinhart, H. L. (1942): J. Biol. Chem., **142**, 921.

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