Nigerian Journal of Paediatrics, **7**(**1**), 26–31

Hereditary Hypophosphataemic Vitamin D-Resistant Rickets

A. A. O. LADITAN* AND G. A. A. OYEMADE†
Departments of Paediatrics and Orthopaedic Surgery†,*
University College Hospital, Ibadan.

Summary

Laditan, A. A. O. and Oyemade, G. A. A. (**1980**). *Nigerian Journal of Paediatrics* **7**(**1**), **26. Hereditary Hypophosphataemic Vitamin D-resistant Rickets.** Three cases of hereditary vitamin D-resistant rickets in a mother, her daughter and son are reported. The three presented with hypophosphataemia, skeletal deformities and dwarfism. The mode of inheritance is thought to be by X-linked dominant transmission or a possible mutation in the mother.

THOUGH the pathogenesis of hereditary hypophosphataemic vitamin D-resistant rickets is unknown, sporadic and familial cases have been reported. In familial cases, the disease is usually inherited as a sex-linked dominant trait (Winters *et al.*, 1958; Burnett *et al.*, 1964); cases occur in both sexes but the clinical manifestations are usually more severe in the males than in the females who may only have hypophosphataemia without overt bone deformity. Other modes of inheritance such as autosomal dominant transmission (Albright, Butler and Bloomberg, 1937; Harrison *et al.*, 1966) and autosomal recessive transmission (Stamp and Baker, 1976), have been demonstrated on rare occasions.

Hypophosphataemic vitamin D-resistant rickets has been reported to be rare among the Negro race (Winters *et al.*, 1958) and to our knowledge no previous case of this type of rickets has been reported in Nigeria. The present communication describes the occurrence of the condition in a Nigerian mother, her son and daughter. We believe that the mode of inheritance of the disease in this family is either by a sex-linked dominant transmission or a new mutation in the mother.

Materials and Methods

Patients

The patients comprised a mother, her daughter and a son, all of whom had overt skeletal deformities. The family pedigree is shown in Fig. I and the relevant clinical and biochemical data on the three patients are summarised in the Table.

Case Reports

Case 1:

F.A., a 40-year old woman, presented at the University College Hospital, Ibadan, in February 1979, with bony deformities. She could not give the exact time of onset of her deformities but said

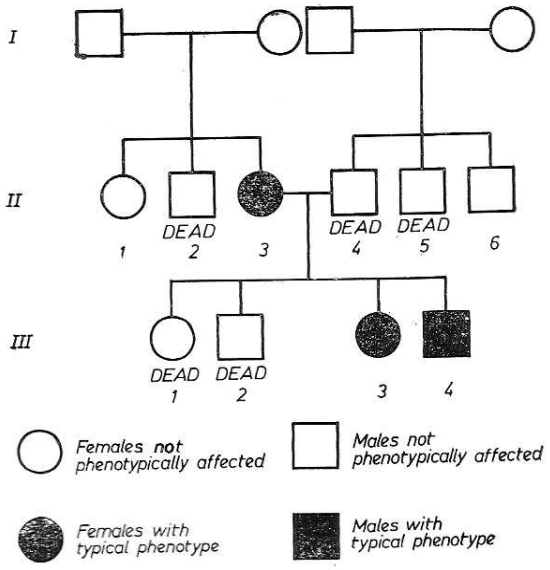

Fig. 1. Pedigree of the Family

that they had been present since her youth and she had received no previous treatment for the deformities.

Physical examination revealed her weight to be 40 kg. and the height to be 148 cm. She walked with a waddling gait, and had mild genu valgus deformity of her left lower limb and anterior bowing of both tibiae (Fig. 2). She was edentulous and claimed that this was due to dental caries during childhood. There was mild swelling of both wrists.

Urinalysis showed no sugar, protein and aminoacids. Serum inorganic phosphate was low while serum calcium, alkaline phosphatase and creatinine levels were normal (Table). The radiographs of the long bones showed evidence of post-rachitic deformities, pseudo-fractures and bony protuberance.

Case 2:

S.A. was a 10-year old daughter of case 1. She had been affected by gross bony deformities since infancy, but her mother did not seek medical care because she thought the deformities would correct themselves with time. Both pregnancy and birth histories were reported to be normal. She was breast-fed for about two years but received no vitamin supplementation.

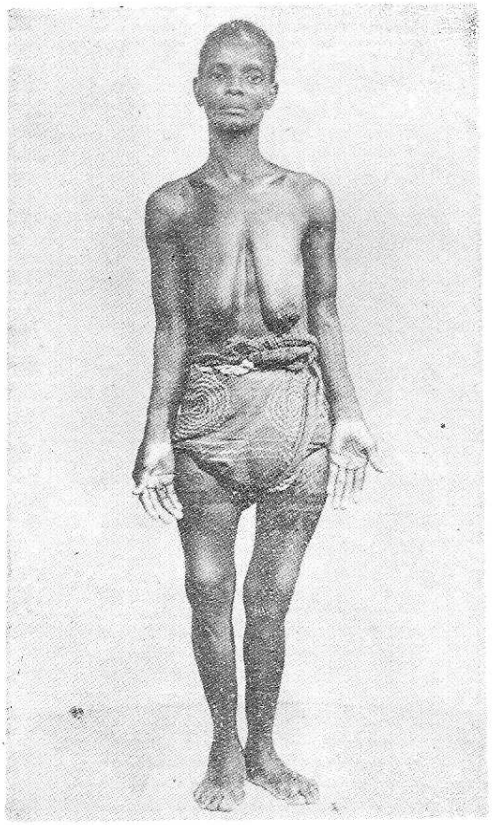

Fig. 2. Photograph of the Mother showing Bost-rachitic Bony Deformities.

Physical examination revealed a very short child for her age. She weighed 17 kg., the height was 99 cm. and the lower limbs were disproportionately short. There was gross anterior bowing of both tibiae and femora with mild bilateral genu varum and marked epiphyseal enlargement of both wrists (Fig. 3). The costochondral junctions were enlarged; the skull was elongated and there was frontal bossing. There was also enamel dysplasia of the lower incisors. The respiratory and cardiovascular systems were normal and no organs were palpable in the abdomen.

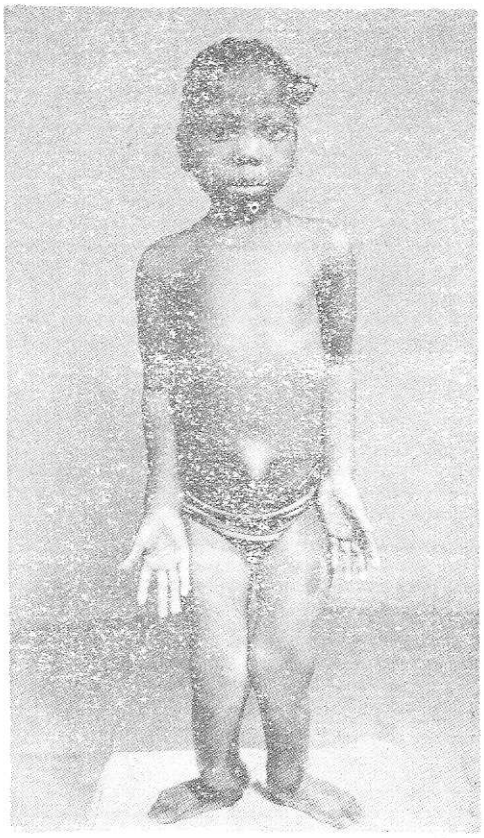

Fig. 3. Photograph of Case 2 showing Short Stature and Deformities of the Upper and Lower Limbs.

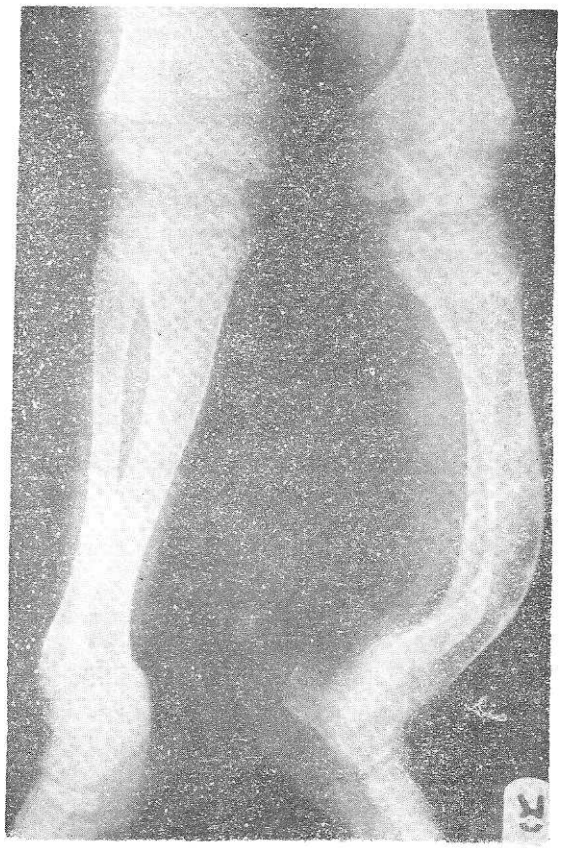

Fig. 4. Radiograph of the Lower Limbs of case 3 showing Rachitic Lesions, Anterior bowing of Tibia and Fibula, and Prominent Harrison's lines in the Tibia.

Laboratory investigations revealed no sugar, protein or aminoacids in the urine. Serum inorganic phosphate was 2.0 mg/100ml; serum calcium 10.0 mg/100 ml; alkaline phosphatase 27 K.A. units/100 ml; creatinine 1.3 mg/100 ml; and urea 10 mg/100 ml. Radiographs of the lower limbs showed rachitic lesions, anterior bowing of tibia and fibula, and prominent Harrison's lines in the tibia (Fig. 4).

Case 3

K.A. was a 5-year old son of case 1. The presenting complaints were the same as those of his 10-year old sibling. Pregnancy, birth and feeding histories were also similar to those of the sibling. He was not immunised against any of the common communicable diseases.

On physical examination, he was very small for his age, and weighed 10.0 kg. The height was 80 cm, and the lower limbs were very short. He walked with a waddling gait. There was anterior bowing of both lower limbs and epiphyseal enlargement at the wrists. The costochondral junctions were also enlarged (Fig. 5). There was hypoplasia of the lower incisors with enamel dysplasia. The respiratory and cardiovascular systems were normal, but there was an enlarged liver of 2 cm and spleen of 7 cm.

The urine was free of sugar, protein and aminoacids. Serum inorganic phosphate was 2.2 mg/100ml; serum alkaline phosphatase 33 K. A. units/100ml; serum calcium 9.6 mg/100ml serum creatinine 1.5 mg/100ml and serum urea; 12 mg/100 ml. The radiograph of the long bones showed evidence of active rickets.

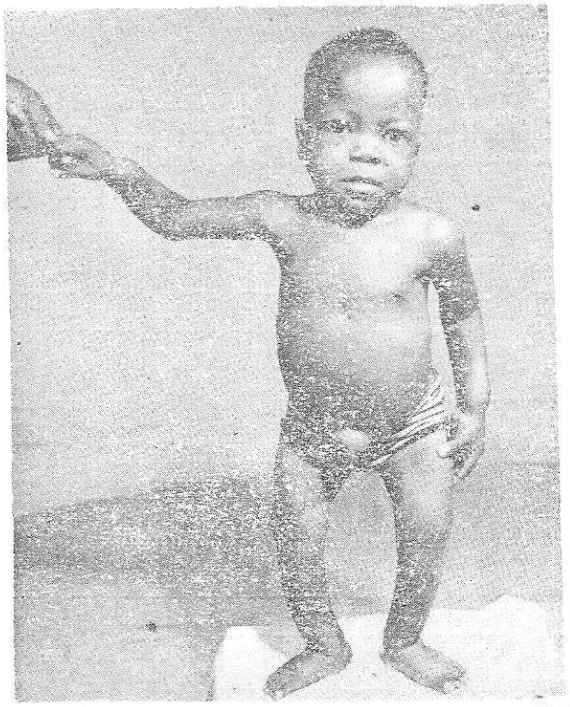

Fig. 5. Photograph of Case 3 showing Short Stature and Rachitic Deformities.

Treatment regimen

The three patients are being treated with inorganic phosphate salt supplement and vitamin D_2 (Calciferol). The inorganic phosphate supplement consists of a mixture of dibasic sodium phosphate (96.0 Gm.) and sodium dihydrogen phosphate (80.7Gm.) dissolved in a litre of water. The mixture is given at a dose of 5 ml five times daily and calciferol is given orally at a dose of 25,000 I.U. per day.

Discussion

Rickets can be classified into three types namely: vitamin D-deficiency, vitamin D-dependent, and vitamin D-resistant rickets. The commonest type in Nigeria is vitamin D-deficiency (nutritional) rickets (Antia, 1971; Laditan and Adeniyi, 1975) while the two other types are rare.

A number of separate entities have been differentiated under the term, vitamin D-resistant rickets and each entity has its specific clinical and biochemical features. Among these entities are the Fanconi syndrome (McCune, Mason and Clarke, 1943), renal tubular acidosis (Lightwood, Payne and Black, 1953), hypophosphatasia (Fraser, 1957) and rickets secondary to steatorrhoea and chronic renal (glomerular) failure (Follis, 1950). However, the most common form of vitamin D-resistant rickets which appears very early in life is that due to hereditary hypophosphataemia. Its diagnostic criteria include the familial occurrence, the presence of rickets or osteomalacia in some but not all affected persons, poor response to the usual doses of vitamin D, hypophosphataemia with normal serum calcium, and diminished gastrointestinal absorption of calcium in affected children (Williams and Winters, 1972). All our three patients presented with hypophosphataemia; the two children had in addition growth failure, delayed dentition and "sitting" deformity of the legs dating to the first year of life, while their mother had post-rachitic deformities.

The genetics of this disorder is not clearly understood. Christensen (1941) described a family of a mother, a son and a daughter with typical rachitic deformities and hypophosphataemia resistant to vitamin D therapy and he regarded the disease as being genetically determined. Subsequent workers later suggested an autosomal dominant mode of inheritance for the disease on the basis of skeletal deformities alone (Mitchell and Mitchell, 1957). However, it was soon realised that some of the affected persons with minimal bony deformities had severe hypophosphataemia and that some healthy relatives of the affected families also had hypophosphataemia. Hypophosphataemia was therefore found to be a better index marker for the disease and with its inheritance from generation to generation, it was thought that hereditary hypophosphataemic vitamin D-resistant rickets was inherited as a sex-linked dominant transmission (Winters *et al.*, 1985

Graham,McFalls and Winters,1959). Since the abnormal gene resides on the X-chromosomes, all the male progeny of an affected male will be normal while his female progeny will all be affected. On the other hand, half of the progeny of an affected female will be normal and half will be affected without regard to sex. The sex-linked dominant hypothesis does not mean that the disorder cannot be transmitted in other ways. Cases have been reported in which both parents as well as all relatives on both sides of the families were clinically and biochemically free from the disorder. Such cases represented either a fresh mutation or a recessive mode of inheritance. In the present report, it is obvious that the mother has transmitted the abnormal gene to her daughter and son but whether she represents a new mutation or a sex-linked dominant disorder would never be known since none of her parents or relatives is alive to be studied.

The prognosis of this condition is good with combined phosphate and vitamin D treatment (West *et al.*, 1964; Glorieux *et al.*, 1972; Mc-Enery, Silverman and West, 1972). The combined chemotherapy brings about an elevation of serum inorganic phosphate to within normal range, heals the rickets, increases linear growth velocity and overcomes dwarfism. A positive correlation between serum inorganic phosphate and growth rate has been reported by Harrison *et al.*, (1966). Although the period of follow-up of our patients so far is short, the prognosis is possibly good because the serum concentration of inorganic phosphate is already beginning to rise.

TABLE

Summary of Clinical and Biochemical Data on Three Patients with Hereditary Hypophosphataemic Vitamin D-Resistant Rickets

Case	*Age (Years)*	*Presenting Features*	*Total serum calcium (mg/ 100 ml)*	*Serum inorganic phosphate (K.A. units/ 100 ml)*	*Serum alkaline phosphatase (mg/ 100 ml)*	*serum electrolytes (mEq/litre)*				*Serum Urea (mg/ 100 ml)*	*Serum creatinine (mg/ 100 ml)*
						sodium	*potassium*	*chloride*	*bicarbonate*		
1.	40	Post-rachitic deformities, dwarfism, waddling gait.	9.9	1.6	10	137	3.7	108	22	18	2.1
2.	10	Gross bony deformities, growth retardation, dwarfism, enamel dysplasia.	10.0	2.0	27	135	3.8	105	19	10	1.3
3.	5	Features of active rickets, hepatosplenomegaly, enamel dysplasia.	6.6	2.2	33	139	3.6	103	23	12	1.5

Acknowledgements

The authors are very grateful to Professors A. U. Antia and J. B. Familusi for their invaluable suggestions during the preparation of this paper; the Medical Illustration Unit of the University of Ibadan for the photographs and also to Mrs F. O. Opatola for typing the script.

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