A CASE OF PSEUDOHYPOPARATHYROIDISM*

S. EPSTEIN, M.B., M.R.C.P., J. SAGEL, M.B., F.C.P. (S.A.) AND W. P. U. JACKSON, M.D., F.R.C.P., *Endocrine Research Group, Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town*

In 1942 Albright and colleagues[1] described the first 3 cases of pseudohypoparathyroidism. This syndrome has come to include patients who have clinical and laboratory evidence of parathyroid insufficiency without evidence of renal disease, steatorrhoea or generalized osteomalacia and with little or no response to parathyroid hormone (end-organ refractoriness). Other diagnostic features[2] include shortening of the metacarpal and metatarsal bones, short thick-set appearance, round facies, and mental retardation. Soft-tissue calcification in subcutaneous areas, basal ganglia calcification, cataracts, and defective and delayed primary or secondary dentition have also been added to the spectrum of features. Up to 1960, approximately 66 cases had been reported in the literature. Recently we had an opportunity to investigate a patient with this syndrome, who subsequently improved after administration of vitamin D.

CASE REPORT

A 12-year-old Coloured girl was referred to Groote Schuur Hospital for investigation of epileptiform seizures and difficulty in swallowing. No history was available from the patient as communication was limited to monosyllabic utterances. However, the history obtained from the mother was as follows; the pregnancy was uneventful with a normal vertex delivery. Her birthweight was 4·5 kg (10 lb). At 2½ years the mother noticed episodes of hyperextension of the head and arching of the back. These attacks occurred on the average of 3 - 4 times per week and persisted unchanged until 10 years of age, at which time the development of flexion of the limbs, incontinence of urine, and transient loss of consciousness was noted. Following these attacks the patient experienced painful cramps in the lower limbs, inability to extend her legs and a refusal to walk. She then adopted a 'Buddha' position. No family history of a similar disease was elicited.

On general examination the patient had a rounded facies, sparse hair, brittle nails and normal digits, without obvious shortening of the metacarpals. The teeth were irregular with ridged and pitted enamel. Chvostek's sign was positive. The right hand was held in a position of flexion of the metacarpophalangeal joints with extension of the interphalangeal joints. Sitting posture was 'Buddha-esque' as shown in Fig. 1.

There was nothing abnormal in the cardiovascular, respiratory and abdominal systems. Examination of the central nervous system showed a retarded patient but accurate assessment of intellect was difficult in view of the limited vocabulary. On ophthalmological examination bilateral lens opacities were found situated peripherally. Papilloedema was not present. No abnormality of the cranial nerves, sensory system and reflexes was obtained. A marked feature was fixed flexure contractions and increased spasticity of the right upper and both lower limbs. Tone was cog-wheel in type at times.

*Date received: 14 October 1970.

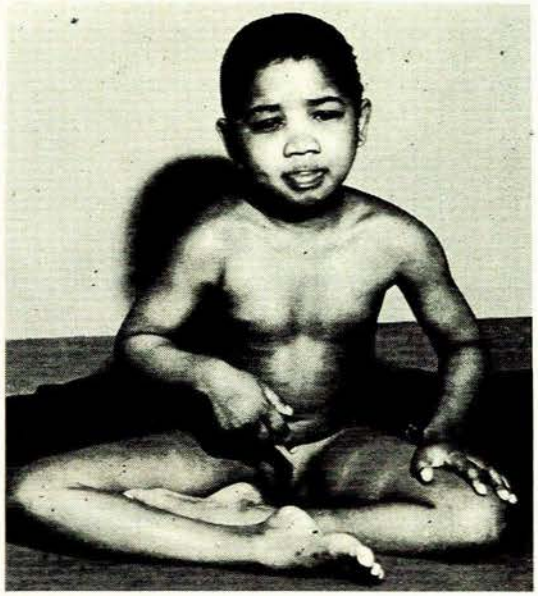

Fig. 1. The typical 'Budda-esque' posture adopted by the patient.

Special investigations. Blood counts, serum proteins and liver function tests were normal. Limited renal function studies showed no impairment. Thyroid function tests were normal. Serum calcium 4 mg/100 ml and 2·2 mg/100 ml (normal 9 - 11 mg/100 ml); serum phosphorus 9·1 mg/100 ml (normal 2·5 - 4·5 mg/100 ml; magnesium 1·15 mEq/litre and 0·94 mEq/litre (normal 1·4 - 2 mEq/litre); alkaline phosphatase 8·4 units (normal 2 - 9 units); cerebrospinal fluid normal. The electro-encephalogram was abnormal—generalized slowing was noted in all areas.

Radiological studies. The skull X-ray showed calcification in the basal ganglia (Fig. 2). In the hands and feet generalized shortening of metacarpal and metatarsal bones with a retarded bone-age of 9 years was apparent. No calcification was seen in the subcutaneous tissue of the lower limbs. X-rays of the teeth showed that the permanent tooth roots were irregularly deformed, blunted and truncated (Fig. 3).

An air-encephalogram confirmed the presence of basal ganglia calcification. In addition cortical atrophy with dilatation of the ventricles was noted.

At this stage because of the clinical features, biochemical and radiological findings, the diagnosis of pseudohypoparathyroidism was entertained. To confirm this the Ellsworth-Howard test was performed. A control subject was taken, and together with our patient given 200 international units of parathormone after baseline urine samples had been collected hourly for 2 hours. The response to parathormone was normal in the control (showing that the preparation was active), but the patient failed to show a phosphate diuresis (Fig. 4) suggesting end-organ refractoriness.

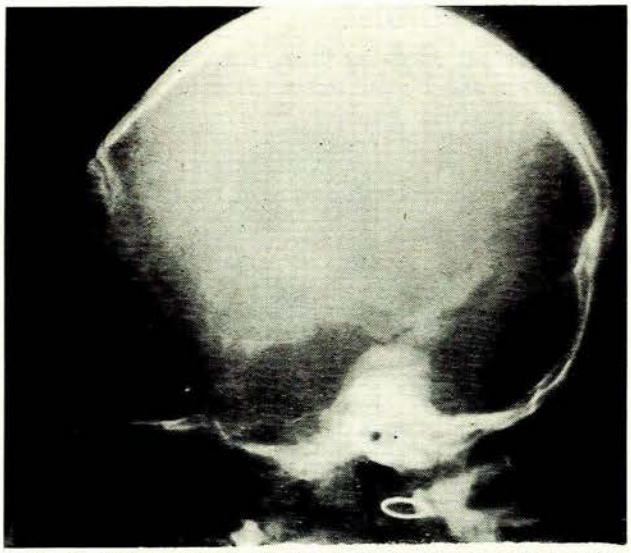

Fig. 2. Lateral X-ray of the skull showing basal ganglia calcification.

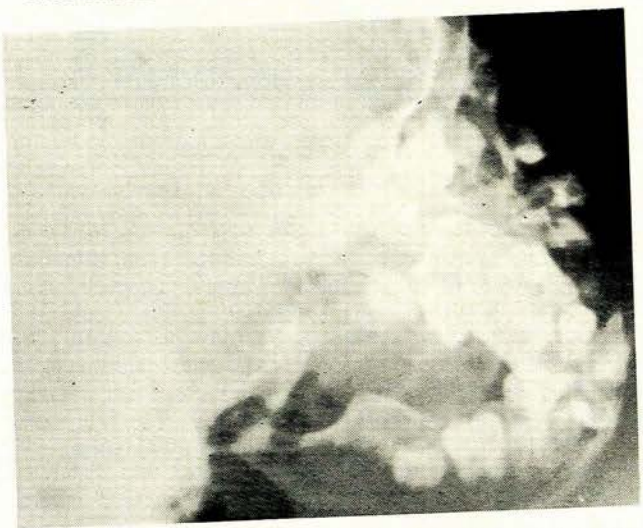

Fig. 3. X-ray of the teeth showing irregularly deformed tooth roots.

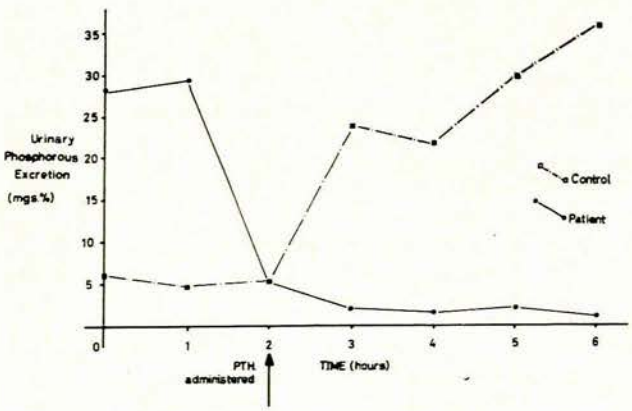

Fig. 4. The effect of parathyroid hormone on phosphorus excretion in a normal subject and our patient (200 IU parathormone given intravenously).

Course and management. During her stay in hospital the patient had two witnessed attacks of spontaneous tetany associated with opisthotonus, laryngeal and carpopedal spasm. These attacks were successfully terminated by intravenous calcium gluconate and intravenous calciferol. Thereafter the patient received 50 000 units of calciferol orally daily. While on therapy, repeat serum chemistry showed an increase of calcium to near normal levels but the phosphorus remained at approximately 10 mg/100 ml. No change in magnesium was seen. In view of the dangers of a high calcium:phosphorus product, aluminium hydroxide was started in order to decrease her serum phosphorus. On therapy it was of interest to note that the function of her upper limbs (especially the right) improved. In addition the alkaline phosphatase increased to 14·4 units.

Because of her persistent deformities and limited mobility of the lower limbs she was referred to the orthopaedic department for corrective procedures.

At follow-up clinic the patient was strikingly improved, mentally more alert, more communicative and had greatly increased mobility. No further episodes of tetanic spasm or epileptiform seizures had been observed by the mother who was delighted with the improvement. Serum calcium eight months after discharge while on 150 000 units of calciferol daily was 8·5 mg/100 ml.

DISCUSSION

Pseudohypoparathyroidism is an uncommon disease and represents end-organ refractoriness to parathyroid hormone. In the cases reported by other workers, the age of presentation has varied from $1\frac{1}{2}$[3] to 51 years of age.[4]

The distinctive clinical features which separate the pseudo-group from the true hypoparathyroid patients are rounded facies, short stature including a short neck, short stubby fingers and obesity—although rarely severe. Our patient exhibited a rounded facies and short stature, but clinically the digits were of normal length and the metacarpals were not short enough to demonstrate the so-called 'Albright's dimple'. In addition mental retardation which is a prominent feature of pseudohypoparathyroidism was also evident in our patient. This mental deficit may be attributable to the hypocalcaemic state with tetany and convulsions. This relationship is not well established, as mental retardation may occur independently of seizures, and normal mentality has also been recorded.[5]

Radiological Findings

The radiological features which have been reported by Cusmano *et al.*[6] include the following: calcification of the basal ganglia, metacarpal and metatarsal shortening, soft-tissue calcification especially in the region of the joints of the extremities, thickening of the calvarium involving all tables, and incomplete development of teeth. Other miscellaneous findings include bowing of the extremities, osteoporosis, exostoses, and accelerated osseous maturation.

Our patient demonstrated calcification in the basal ganglia, irregular abnormal dentition, rarefaction of the bones and shortened metacarpals and metatarsals.

Biochemical Findings

The most consistent biochemical findings are hypocalcaemia and hyperphosphataemia. In pseudopseudohypo-

parathyroidism where the patients phenotypically mimic pseudohypoparathyroidism, the serum calcium and phosphorus are normal. The alkaline phosphatase is inconsistently elevated and was normal in our patient. In her case the enzyme increased with therapy. Evidence of end-organ unresponsiveness characteristic of pseudohypoparathyroidism is demonstrated by the Ellsworth-Howard test.[7] The excretion of phosphorus is measured following an intravenous injection of 200 units (2 ml) of parathormone (Lilly) to a fasting subject and control. Normal subjects respond with a 2 - 6-fold increase (depending upon preparation) in phosphorus excretion within the first 3 hours after injection. Primary hypoparathyroid patients show up to a 10-fold increase in phosphorus excretion. In pseudohypoparathyroidism there is no significant change in the urine excretion of phosphorus and in fact the urinary excretion dropped in our patient. The control subject responded to the administered parathormone indicating activity of the particular preparation (Fig. 4).

The aetiology of the hypocalcaemia has been attributed to various mechanisms. These include the presence of a binding or inhibiting substance in the serum to parathormone; decreased or absent production of biologically active parathormone by the parathyroids; production of abnormal or biologically ineffective parathyroid hormone; and end-organ refractoriness. In addition a high thyrocalcitonin content in the thyroid has been found in these patients and the role of excess thyrocalcitonin has been speculated upon. The storage of thyrocalcitonin may merely be a reflection of prolonged hypocalcaemia.

Application of radio-immunoassay for parathyroid hormone has shown that in pseudohypoparathyroidism the values of the hormone are increased 2 - 5-fold as compared with normals.[8] This indicates that secretion, far from being diminished as in primary hypoparathyroidism, is in fact increased. Evidence of end-organ refractoriness to administered parathormone has been demonstrated by an absence of cyclic 3′ 5′ adenosine monophosphate (3′ 5′ AMP) in the urine. The normal renal response to parathormone is the rapid excretion of cyclic AMP, an effect that precedes and may mediate the phosphoturic effect of parathormone.[9] This implies a renal cellular membrane defect.

Relationship to Other Disorders

The coexistence of hypothyroidism and pseudohypoparathyroidism has been well documented.[10] This may be due to isolated thyrotropin deficiency in some cases.[11] Clinically, the short stature, mental retardation and slow deliberate movements are common to both conditions and provide no distinction; laboratory investigation may be needed to clinch the diagnosis. The thyroid function studies in our patient were all normal.

Recently the occurrence of gastro-enteritis in pseudohypoparathyroidism has demonstrated an associated deficiency of intestinal lactase.[12]

Therapy

Vitamin D is the treatment of choice. This can be in the form of calciferol or dihydrotachysterol (old preparation AT 10). Dosage varies from individual to individual as does the response. The response to therapy in patients with tetany is usually dramatic. Oberst and Thompkins[3] observed significant improvement in mental state although this is not a universal experience. Our patient's general well-being improved considerably on therapy with vitamin D and she became less withdrawn and more willing to co-operate. Repeated serum calcium estimations are important to prevent the occurrence of hypercalcaemia while on therapy. Likewise aluminium hydroxide may be necessary to counteract the high serum phosphorus. Other drugs which have been used are probenecid[6] and acetozolamide, in an attempt to inhibit tubular reabsorption of phosphorus by direct effect on the renal tubules. Recently it has been reported that parathormone given concurrently with vitamin D_2 has been effective in the treatment of pseudohypoparathyroidism.[13]

SUMMARY

A case of pseudohypoparathyroidism is described. This condition, due to end-organ unresponsiveness to parathyroid hormone, manifests by mental retardation, short thick-set appearance, with rounded facies and characteristic bony abnormalities. In addition the patient demonstrated basal ganglion calcification and abnormal dentition, features which are not unusual. Biochemical investigation showed a low serum calcium with a high serum phosphorus level. The administration of exogenous parathormone failed to promote a phosphate diuresis, confirming end-organ refractoriness. A striking improvement was noted on the administration of calciferol.

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