PSEUDOHYPOPARATHYROIDISM: REPORT OF A CASE

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Pseudohypoparathyroidism is a rare syndrome first described by F. Albright, Burnett, Smith and Parson in 1942. Since then it has been described under various names: Albright's syndrome, Albright's hereditary osteodystrophy, Albright's osteodystrophy, Seabright-bantam syndrome and Brachy-metacarpal Dwarfism.

Patients with pseudohypoparathyroidism have similar symptoms, signs and biochemical abnormalities as those with hypoparathyroidism, but instead of being deficient in parathyroid hormone, they produce normal amounts of the hormone but are unable to respond to it. In addition they have certain distinctive clinical features and abnormalities which differentiate them from patients with hypoparathyroidism and which help in establishing the diagnosis. These include mental retardation, a round face, a short stature, strabismus, brachydactylia (especially of the metacarpal and metatarsal bones) soft tissue calcification and enamel hypoplasia.

In 1952, Albright, Forbes and Henneman reported a patient who showed physical findings similar to pseudohypoparathyroidism but had no chemical or physiological abnormalities. Because of her physical appearance the disease was termed pseudo-pseudohypoparathyroidism.

Since the original description, about 70 cases of pseudohypoparathyroidism (Cohen et al., 1960) and 40 cases of pseudo-pseudohypoparathyroidism (Papaioannou and Matsas, 1963) have been reported in the literature. Considerable difference of opinion exists regarding the existence of pseudo-pseudohypoparathyroidism as a distinct entity apart from pseudohypoparathyroidism.

As far as we are aware, a case of pseudohypoparathyroidism has not been reported in the local literature. We report below such a case.

CASE REPORT

Y.F.O., a 19 year old Chinese (Cantonese) girl who was first seen in September 1966 when she complained of painful swelling of her right knee joint and swelling of both legs of 3 months duration. She had not menstruated yet at time of admission. There was no history of convulsions, acral paraesthesia, carpal spasma, visual impairment, headaches or skeletal symptoms. She did not have any significant gastrointestinal symptoms or a history of kidney disease.

She was a full term, normally delivered baby. There was no maternal illness during pregnancy. Her birth weight was 6 lbs. "Milestones" were apparently normal. She is the 3rd child in a family of 3 girls and 1 boy. None in the family resembled patient's appearance. She is mentally slow, with a subnormal I.Q.

Her height is 60 inches and she weighs 79 pounds. Her face is roundish, eyes hyperteleoric and she has a vacant expression (Fig. 1). She developed an erythematous, maculo-papular and scaly butterfly rash over her face while in hospital. There is no cataract or lenticular opacities. The fundi are normal. She had extensive caries and when seen by the dental surgeon was found to have evidence of enamel hypoplasia.

Her hands and feet are generally small; the digits are short particularly the ring and little

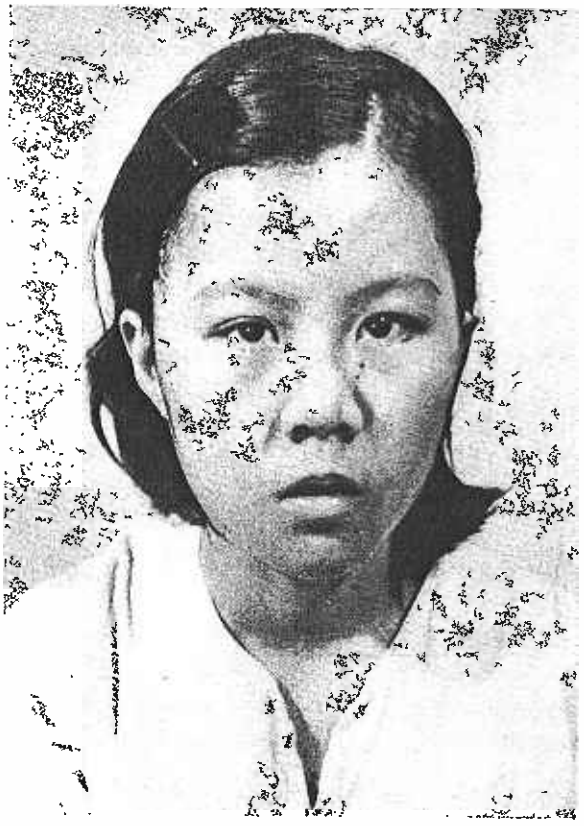

Fig. 1. Showing patient's face with hyperteleoric eyes and vacant expression.

fingers and the 2nd to 5th toes (Fig. 2). The knuckles over her ring and little fingers are small and inconspicuous (Fig. 3). The skin over her palms and soles are atrophic. There were no obvious dermatoglyphic abnormalities. Her arms show a slight increase in the carrying angle (cubitus valgus) but there is no webbing of the neck. Careful search over the body revealed no subcutaneous plaques. The thyroid and parathyroid glands are not palpable.

Her blood pressure is 110/70. She has extra systoles intermittently. The liver and spleen are just palpable. The axillary and pubic hair are present but scanty and there is poor breast development. She has generalised hyper-reflexia but Chvostek's and Trousseau's signs are absent.

Haematological examination revealed a haemoglobin value of 11 grams%, a white blood cell count of 9800 with a normal differential count and a platelet count of 230,000. The E.S.R. was 78 mm/hour, blood urea 20 mgm%, serum calcium (blood taken without torniquet) varied from 7·8 to 9·0 mgm% (normal values being 9 to 11 mgm%) and inorganic phosphate of 4·0 to 5·0 mgm% (normal values from 3 to 4·5 mgm%). Serum protein by electrophoresis gave a value of 7·5 gms% with albumin 4·0 gm%; alpha-1-globulin 0·1 gm%, alpha-2-globulin 0·9 gm%; beta globulin 0·7 gm% and gamma globulin 1·8 gm%. The serum alkaline phosphatase was 6·6 King Armstrong units. The rheumatoid arthritis test was positive and blood for lupus erythematosus cell was also positive. The glucose tolerance test was normal.

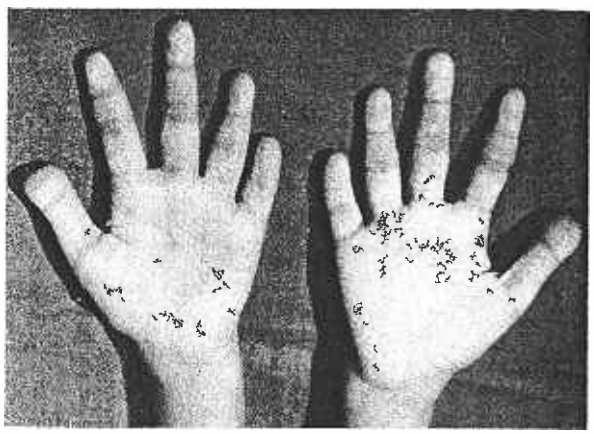

Fig. 2a.

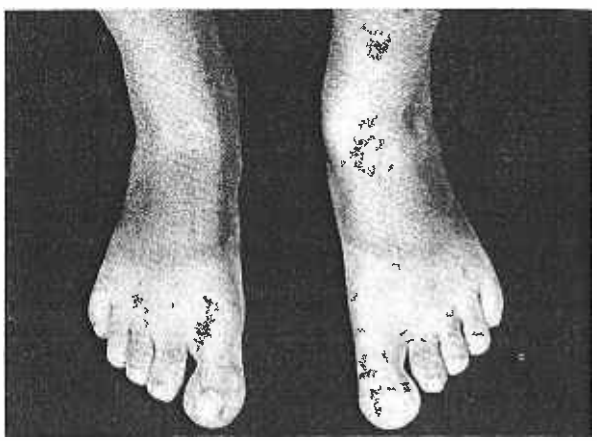

Fig. 2b.

Figs. 2a & 2b. Showing the typically short fingers and toes particularly the ring and little fingers and the 2nd toes.

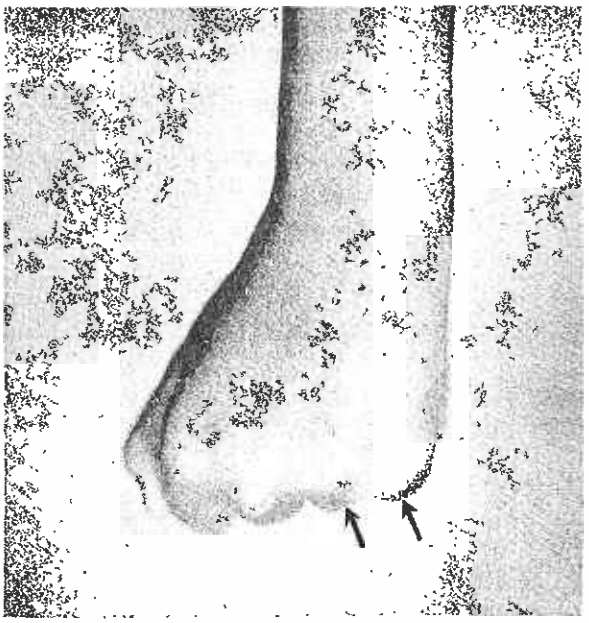

Fig. 3a.

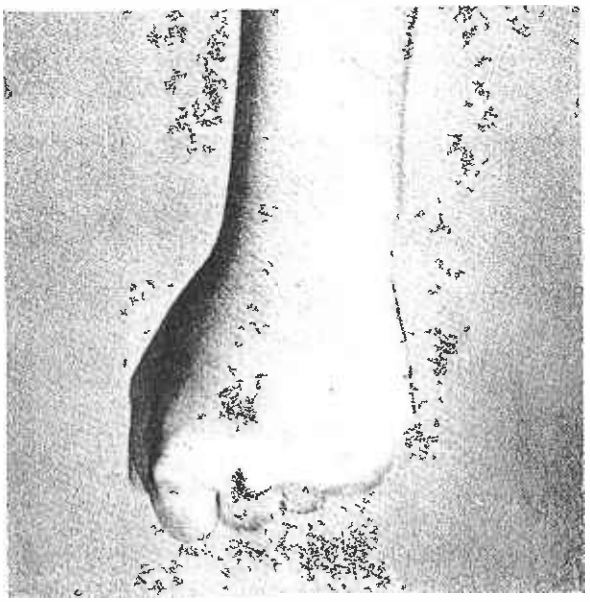

Fig. 3b.

Figs. 3a & 3b. Showing the small knuckles over the ring and little fingers of the patient's clenched fist (Fig. 3a) compared with those of her sister's knuckles seen in Fig. 3b.

Urinalysis showed no albumin or sugar and microscopic examination of the urine was normal. A 24-hour collection of urine was estimated for urinary steroids and results gave values of 0·7 mgm per day for 17 ketosteroids and 4·1 mgm per day for 17 hydroxycorticosteroids, which rose to 2·4 mgm per day and 12·8 mgm per day respectively following an intravenous infusion of 25 units of crystalline ACTH in a pint of normal saline over 8 hours. These values are on the low side. Urinary calcium and inorganic phosphate over 24 hours were 78 mgm and 240 mgm respectively on a normal diet.

A skeletal survey was done but did not show any evidence of soft tissue calcification. Roentgenogram of skull showed brachycephaly; the vault thickness being normal and no intracranial calcification was seen. Roentgenogram of the hands showed brachydactylia, with disproportionate shortening involving the 4th and 5th metacarpals, the intermediate phalanges of 2nd, 4th and 5th digits and the terminal phalanges of the 1st digit (Fig. 4). Roentgenograms of the

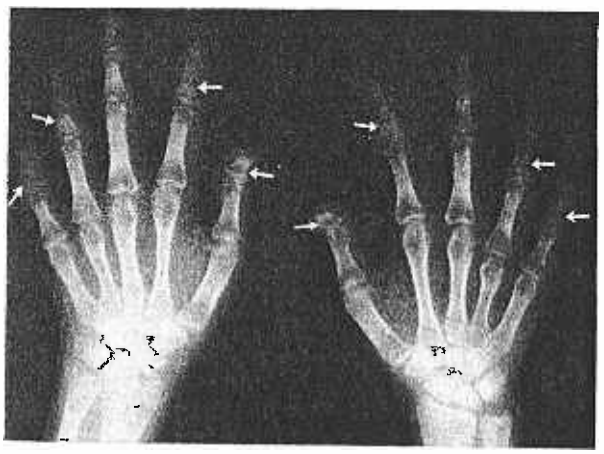

Fig. 4. Roentgenograms of the hands showing brachydactylia with disproportionate shortening involving the 4th & 5th metacarpals; the intermediate phalanges of the 2nd, 4th & 5th digits and the terminal phalanges of the 1st digit.

feet showed general shortening of the tubular bones of 2nd, 3rd, 4th and 5th digits and their metatarsals especially the proximal phalanges which account for the obvious shortening of the toes (Fig. 5). The changes are symmetrical in both the hands and the feet.

Buccal smears were taken and chromatin sex was positive (20%). Electrocardiogram showed multiple extrasystoles intermittently but was otherwise normal. Electroencephalogram was normal. Thyroid function tests were normal with a basal metabolic rate of plus 10% (Dubois) and a protein bound iodine of 6·5 micrograms%.

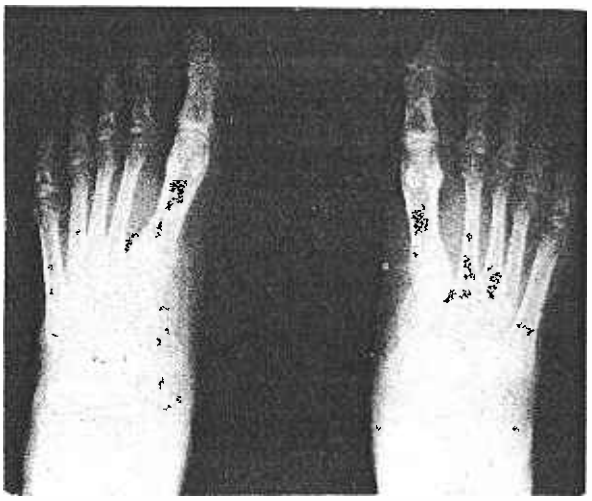

Fig. 5. Roentgenograms of the feet showing shortened phalanges and metatarsals of the 2nd, 3rd, 4th, & 5th digits.

DISCUSSION

The diagnosis of pseudohypoparathyroidism is usually suspected when the patient is noted to be short, stocky, round faced, mentally retarded and to have brachymetacarpy, brachymetatarsy and enamel hypoplasia (all these features were present in this patient). Other features of pseudohypoparathyroidism such as history of convulsions, cramps and paraesthesia, subcutaneous calcifications, bony exostoses, cataracts, lenticular opacities and positive Chvostek's and Trousseau's sign are not seen in this patient. Laboratory investigations reveal hypocalcaemia and hyperphosphataemia (in this patient, the serum calcium was low and the serum inorganic phosphate was on the high side of normality). Roentgenography confirms the clinical suspicion of bony abnormalities, and in addition may reveal basal ganglia calcifications, thickened calvarium, osteoporosis and/or osteosclerosis.

In the years since the original diagnostic criteria were proposed, it has become apparent that a previously hypocalcaemic patient may become normocalcaemic during periods of decelerated bone growth. (Gershberg and Weseley, 1960). Thus normocalcaemia does not eliminate the diagnosis of pseudohypoparathyroidism and it may be necessary to study the patient's response to intravenous parathyroid hormone which is the basis of the Ellsworth-Howard Test (Ellsworth and Howard, 1934). Generally with this test, patients with pseudohypoparathyroidism show only a two-fold rise in urinary phosphate excretion, while patients with hypoparathyroidism or pseudo-pseudohypoparathyroidism show a ten-fold rise and normal patients show a five to six fold rise. How-

ever, not all the diagnosis of pseudohypoparathyroidism have been confirmed by proving them unresponsive to exogenous parathyroid hormone. There appear to be many cases reported which have not given the expected response and recent experience with this test suggests that it is not very helpful in differentiating pseudohypoparathyroidism from idiopathic hypoparathryroidism (Williams, 1962). A better test to differentiate hypoparathyroidism and pseudo-hypoparathyroidism is to give 100 to 200 units of parathormone every 6 hours for 3-4 days. In cases of true hypoparathyroidism this causes a marked decrease of serum phosphorus and rise of serum calcium while in pseudohypoparathyroidism the phosphorus does not fall (Wilkins, 1965). We have not performed this test on our patient as we were unable to obtain parathyroid hormone at the time of writing.

Pseudo-pseudohypoparathyroidism differs from pseudohypoparathyroidism in that the blood chemistry is normal and the response to exogenous parathyroid hormone is normal (Ellsworth and Howard, 1934). Also a history of seizures, enamel hypoplasia, basal ganglia calcification and osteoporosis are absent in pseudo-pseudohypoparathyroidism.

This patient also has lupus erythematosus as evidenced by the presence of "butterfly" rash, high E.S.R., hypergamma-globulinemia, positive Rheumatoid Arthritis test and presence of L.E. cells. As far as we are aware, such a case of lupus erythematosus in a patient with pseudohypoparathyroidism, has not been described in the literature before.

Chromosomal abnormalities (one large acrocentric chromosone, probably No. 15, which possessed usually massive short arm with prominent satellites) have been described in a patient with pseudo-pseudohypoparathyroidism by Jancar (1965).

In a recent review, Mann et al (1962) described the various features that may be seen in pseudohypoparathyroidism and pseudo-pseudohypoparathyroidism and these are shown in Table I.

TABLE I

SHOWING MANIFESTATIONS OF PSEUDOHYPOPARATHYROIDISM AND PSEUDO-PSEUDOHYPOPARATHYROIDISM

(after Joel B. Mann, Alterman, S., and Gorman Hills, A., 1962.)

A. ALWAYS PRESENT IN PH
1. Hypocalcemia*
2. Resistance to hypercalcemic effect of daily intra-muscular injections of parathyroid extract**

B. USUALLY PRESENT IN PH
1. Hyperphosphatemia*
2. Basal ganglia calcification
3. History of tetany or convulsions

C. USUALLY PRESENT IN PH AND PPH
1. Metacarpal or metatarsal abnormalities or both*
2. Short stature (less than 60 inches)*
3. Round face*
4. Subcutaneous calcification or ossification or both
5. Dental aplasia or delayed dentition*

D. OFTEN PRESENT IN PH AND PPH
1. Family history suggestive of some related abnormalities
2. Mental retardation*
3. Exostoses
4. Lenticular calcification
5. Thickened calvarium

E. OCCASIONALLY PRESENT IN PH AND PPH
1. Endocrinopathies
   a) Diabetes mellitus (latent or overt)
   b) Hypothyroidism
   c) Low 17-ketosteroid excretion*
   d) Delayed puberty*
   e) Hypomenorrhea*
   f) Diabetes insipidus
2. Genu valgum
3. Radius curvus*
4. Blue sclerae
5. Gonadal dysgenesis

*Denotes features present in our patient
**This test was not done
PH = Pseudohypoparathyroidism
PPH = Pseudo-pseudohypoparathyroidism

The aetiology of pseudohypoparathyroidism is unknown. The syndrome is apparently a congenital and familial one and other congenital abnormalities such as stunted growth, mental retardation, round facies and brachydactylia are associated with it. It is believed that in pseudohypoparathyroidism the parathyroid glands secrete their hormone normally but the renal tubules controlling the reabsorption of phosphorus do not respond to it. It is of interest that resistance of an end organ to a hormone is encountered in a number of other "pseudo-endocrinopathies" *e.g.* in pitressin-resistant diabetes insipidus (nephrogenic diabetes insipidus) who show no response to pitressin therapy, and in certain intersexes who have absent sexual hair in spite of a normal secretion of androgen (Wilkins, 1965). Lowe (1950) has produced evidence that while parathyroid hormone fails to increase the renal excretion of phosphorus in these patients, it does increase serum calcium. Treatment with dihydrotachysterol (A.T. 10) or with large doses of vitamin D corrects the disorder.

SUMMARY

A case of pseudohypoparathyroidism is described. This patient also has lupus erythematosus. The association of these two conditions has not been described before. The diverse features of pseudohypoparathyroidism and pseudo-pseudohypoparathyroidism and their diagnoses are discussed.

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