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BRACHYMETACARPAL DWARFISM OR PSEUDO-PSEUDOHYPOPARATHYROIDISM WITH MENTAL DEFECT IN SIBLINGS

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BRACHYMETACARPAL dwarfism or pseudo-pseudohypoparathyroidism is a rare condition characterized essentially by short metacarpals and reduced stature, features shared in common with pseudohypoparathyroidism. The latter was believed by Elrick et al.[1] to arise from mutation of a gene controlling several traits. Elrick and his colleagues suggested that three separate disturbances were involved, and described the following: failure of the parathyroid end-organ to respond to parathyroid hormone, ectopic ossification in the soft tissues, and dyschondroplasia. In the first disturbance, in which the renal tubule is resistant to the effects of parathormone, failure to decrease the reabsorption of phosphorus, with resultant upset of calcium-phosphorus balance, leads to hypocalcemia with its attendant train of symptoms. These include the various manifestations of tetany. The patient may complain merely of tingling sensations in the extremities, or muscle cramps, stiffness and fatigue. Twitching of muscles, carpopedal spasm or laryngospasm may occur. A positive Chvostek sign has been reported in rather more than half and a positive Trousseau sign in rather less than half the cases. Frame and Carter[2] stressed the occurrence of frank convulsions in two-thirds of recorded cases of pseudohypoparathyroidism. They noted that these were for the most part typical grand mal seizures, with an age of onset varying from two weeks to eighteen years. Trophic changes may be present. The skin may be dry, rough and scaly and the nails brittle and thickened. The hair of the scalp may be coarse and sparse and there may be loss of eyebrows and eyelashes. Lenticular opacities have been noted in some and the teeth may exhibit transverse ridging or they may fail to erupt. On biochemical examination values of serum calcium and serum phosphorus are found to be similar to those in idiopathic hypoparathyroidism. In their review of 25 cases of pseudohypoparathyroidism, Frame and Carter found a range of serum calcium from 4.3 mg. % to 9.2 mg. %, with an average serum level of 6.8 mg. %, compared with a normal range of 9 to 11 mg. %. They similarly noted a range of serum phosphorus from 4.2 mg. % to 11.1 mg. %, with an average serum level of 7.5 mg. %, compared with normal values of 2 to 4 mg. %. Radiologically, bone density is usually normal or even slightly increased, although a number of cases have been recorded with skeletal demineralization. Calcification is commonly present in the basal ganglia, either in punctate fashion or as radiating striations.

Deposition of calcium in the soft tissues is commonest in the neighbourhood of joints, and the pathology includes actual bone formation as well as the laying down of subcutaneous nodules or plaques of calcium. Subcutaneous ossification has occasionally been noted at birth; in other cases it has made its appearance considerably later in life. Ossification may also take place in bursae and muscles.

The dyschondroplasia of pseudohypoparathyroidism is characterized by short, thick-set stature, rounded facies and anomalies of the metacarpals and metatarsals. The latter become manifest as abnormal shortening of one or more of the fingers or toes. Fingers are most commonly involved. In their review, Frame and Carter noted that in 13 cases at least one finger was abnormally short, whereas in three cases abnormally short toes were present in addition to the short fingers. Metacarpals I, IV and V, and metatarsals I and V are chiefly affected. These bones are disproportionately short and are often wider than normal. Occasionally the phalanges are shortened and widened. Further features sometimes present include bowing of the fibula, spur formation on the tibia, coxa valga and widening of the medullary cavities of the long bones.

In most cases of pseudohypoparathyroidism the occurrence of intellectual retardation has been mentioned. Frame and Carter observed evidence in a number of cases that intellectual retardation had existed from infancy and that in others it had clearly antedated the onset of seizures. MacGillivray[3] observed that intellectual retardation had been present in 21 of 22 cases where the mental state had been remarked upon.

The term pseudo-pseudohypoparathyroidism was first applied by Albright, Forbes and Henneman[4] to a patient with dyschondroplasia and ectopic ossification alone. The patient had all the appearance of pseudohypoparathyroidism save that there were no biochemical manifestations indicating hypoparathyroidism, such as tetany, hyperphosphatemia or hypocalcemia. Initially the terms suggested were a-hyperphosphatemicpseudohypoparathyroidism, or a-hypocalcemicpseudohypoparathyroidism, but finally pseudo-pseudohypoparathyroidism was decided upon. Since then additional cases have been described, and recently Van der Werff ten Bosch[5] reviewed a total of 14 cases in the literature, including a number of his own. In only three instances did he find subcutaneous calcinosis or ectopic ossification, from which he concluded that this feature was not an essential feature of pseudo-pseudohypoparathyroidism. On the other hand, peculiarities common to all cases were reduced stature and shortness of the lateral metacarpals.

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Van der Werff ten Bosch considered that the term should be reserved for patients of short stature, with shortness of the lateral metacarpals but without tetany. Noting the frequency of menstrual disorders he was also inclined to believe that gonadal dysgenesis might sometimes be associated with the syndrome.

The following three sisters with reduced stature, metacarpal shortening and mental defect were admitted to the Manitoba School in 1926.

CASE 1.—This patient, aged 50 years, was the eldest of the sisters. Little is known of the family history. Both parents were born abroad and both died of influenza during the 1919 pandemic. The paternal grandparents were said to have been of normal physical and mental health. Nothing is known of the maternal grandparents. A paternal aunt and three cousins were reported to be normal physically and mentally. In the patient's own family a fourth sister was believed to have been of subnormal intelligence. The patient herself was cared for in a public institution until 1926. In that year, at the age of 16, she was admitted to the Manitoba School. The remaining sibling, an apparently normal brother, escorted the patient and her two sisters when they were admitted. He was unable to supply information about their early development beyond the fact that they had been retarded from infancy and had not been able to benefit from schooling.

Physically the patient was a squat woman with rounded facies and skull. Her height was 144 cm., span 145 cm., and weight 114 lb. Her hands were short and broad. Her nails and teeth appeared normal. The texture of her skin and hair was normal. Her acuity of vision was fair. Right-sided oculomotor paresis was present, her hearing was impaired, and her speech was an unintelligible jargon. Chvostek and Trousseau signs were negative. Her blood pressure was 100/60 mm. Hg. Serum calcium was 10.4 mg. %, serum phosphorus 2.0 mg. %, serum alkaline phosphatase 4.71 King-Armstrong units, and total proteins 6.4 g. %. On radiological examination, there was shortening of the metacarpals generally, but more especially of metacarpals IV and V. A small simple cavity formation was present in the right scaphoid. There was no evidence of calcinosis or ectopic ossification. Her intelligence was within the imbecile range, her I.Q. being 30.

CASE 2.—This patient was aged 47 years. Her facies was broad and her build thickset and stocky. Her height was 151 cm., span 150 cm., and weight 124 lb. Her hands were short and broad. The nails, skin and hair were normal. Her lower teeth were crowded and irregular. Acuity of vision was normal. Chvostek and Trousseau signs were negative. Her blood pressure was 100/64 mm. Hg. Serum calcium was 10.7 mg. %, serum phosphorus 3.36 mg. %, serum alkaline phosphatase 4.28 K.-A. units, and total proteins 6.89 g. %. Radiological examination showed appreciable shortening of the metacarpals, more especially of metacarpals IV and V; metacarpal V was also as broad as metacarpal I. There was no evidence of calcinosis or ectopic ossification. Her I.Q. was 33. A thyroidectomy scar was present; the patient was reported to have had a goitre removed prior to admission.

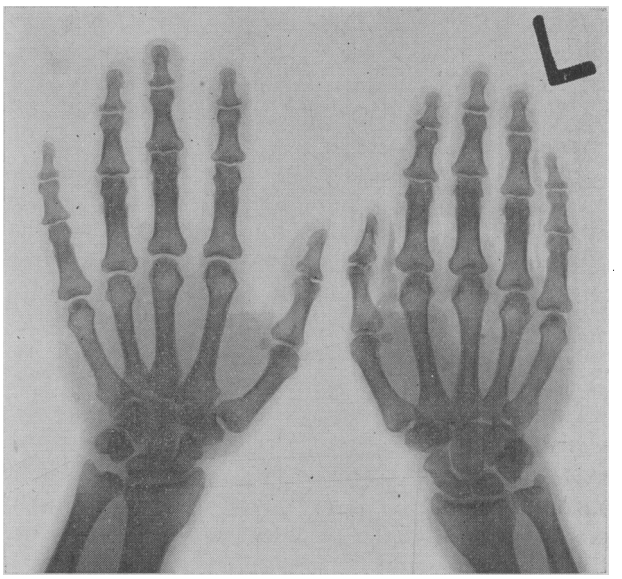

Fig. 1.—(Case 2) Shortening and broadening of metacarpal V.

CASE 3.—The third patient was 43 years of age. Her build was thickset and stocky, with rounded face and receding chin. Her height was 144 cm., span 140 cm., and weight 124 lb. The hands were short and broad and the tips of the fingers were slightly bulbous. Her nails, hair and skin were normal. The teeth were fairly normal. Her acuity of vision was normal. Chvostek and Trousseau signs were negative. Her blood pressure was 106/70 mm. Hg. Serum calcium was 9.4 mg. %, serum phosphorus 2.0 mg. %, serum alkaline phosphatase 7.28 K.-A. units, and total proteins 6.4 g. %. Radiologically metacarpals IV and V were disproportionately short and the phalanges also showed a greater width than normal. There was no evidence of calcinosis or ectopic ossification. Like her sisters, her intelligence was within the imbecile range, her I.Q. being 26. Her history showed that she also had severe dysmenorrhea for many years and that subtotal hysterectomy was carried out in 1956 for the removal of cystic ovaries and fibroid uterus.

DISCUSSION

The three cases presented have been characterized by reduced stature, rounded or broad face and anomalies of the metacarpals, more especially shortening of metacarpals IV and V, with or without an accompanying broadening. No patient presented evidence of tetany, and the serum calcium and serum phosphorus were within normal limits. The conditions would thus appear to correspond to the syndrome of pseudo-pseudohypoparathyroidism or brachymetacarpal dwarfism as defined by Van der Werff ten Bosch. All three were women, in keeping with the same author's finding of a predominantly female incidence. A familial incidence has already been reported by Seringe and Tomkiewicz[6].

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Intellectual retardation was present from an early age and all patients were of imbecile grade. Impaired intelligence can be a feature of both idiopathic hypoparathyroidism and pseudohypoparathyroidism. Idiopathic hypoparathyroidism may be associated with backwardness in young people[7] and with dementia in older subjects[8]. The reversible nature of the dementia after restoration of the serum calcium to normal suggests that in some cases at least the mental state is a direct result of hypocalcemia. Also in a number of instances of pseudohypoparathyroidism, improved mental state has followed administration of calciferol or dihydrotachysterol to raise the serum calcium to normal levels[9]. In other instances, however, intellectual retardation is permanent and irreversible. The presence of intellectual retardation from an early age and the absence of progressive deterioration in such cases would tend to indicate a basic amentia. In view of the recorded prevalence of intellectual retardation in pseudohypoparathyroidism, it would not be surprising to find it occurring in the closely allied state of pseudo-pseudohypoparathyroidism or brachymetacarpal dwarfism, and hence to find instances of this unusual condition in institutions for the mentally defective.

In the diagnosis of brachymetacarpal dwarfism, there are, quite apart from pseudohypoparathyroidism, a number of equally rare diseases associated with abnormality of the metacarpals, but only fortuitously associated with mental defect. They include the Marchesani syndrome, familial brachydactyly and myositis ossificans progressiva.

In the Marchesani or Weill-Marchesani syndrome, short stature and brachydactyly are combined with spherophakia. The small spherical lens of spherophakia gives rise at an early age to high myopia and glaucoma, and hence most cases of the syndrome are likely to be seen initially by ophthalmologists. Brachydactyly is severe and the hands are strikingly small. Symmetrical shortening and widening of metacarpals and phalanges is associated with marked retardation in carpal ossification. The thick palms and short, stumpy fingers, wide at their bases, result in a trident-shaped hand. In the two cases described by Zabriskie and Reisman[10] there was inability to flex the fingers completely or make a fist. Short feet and toes may also occur. Mental defect does not appear to be an associated feature. The condition is hereditary and Falls[11] suggests that an autosomal recessive gene is responsible, although incomplete dominance is a possibility in some instances. Recently Bowers[12] has recorded the first instances of the syndrome in Canada, in a sibship where arachnodactyly was also present.

Familial brachydactyly is a dominant condition, first described in detail by Brailsford[13]. Both fingers and toes are generally affected, and short stature may be an accompaniment. Deformity is the result of a number of skeletal anomalies. These include broadening and shortening of the terminal, medial and proximal phalanges, total or partial absence of phalanges, and shortening of metacarpals and metatarsals. The terminal phalanx of the thumb may be exceptionally short, the short first metatarsal may be deformed by exostosis, and middle and terminal phalanges of the little toes may be fused. Serum calcium and phosphorus are not altered.

In myositis ossificans progressiva shortening of digits is generally limited to thumbs and great toes. Deformity of the distal ends of the first metatarsals is apt to result in hallux valgus. Serum calcium and phosphorus are unaltered. Apart from brachydactyly the disease is characterized by slowly progressive ectopic calcification, setting in mainly during the first decade, principally in males, and leading to increasing stiffness from ossification in affected muscles and related structures.

SUMMARY

Three cases of brachymetacarpal dwarfism or pseudopseudohypoparathyroidism have been described in siblings. Shortness of stature was associated with shortness of the lateral metacarpals and absence of tetany. In each case intellectual retardation was an additional feature.

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REFERENCES

1. ELRICK, H. *et al.*: *Acta endocrinol.*, **5**: 199, 1950.
2. FRAME, B. AND CARTER, S.: *Neurology*, **5**: 297, 1955.
3. MACGILLIVRAY, R. C.: *Am. J. Ment. Deficiency*, **62**: 861, 1958.
4. ALBRIGHT, F., FORBES, A. P. AND HENNEMAN, P. H.: *Tr. A. Am. Physicians*, **65**: 337, 1952.
5. VAN DER WERFF TEN BOSCH, J. J.: *Lancet*, **1**: 69, 1959.
6. SERINGE, P. J. AND TOMKIEWICZ, S.: *Semaine Hôp. Paris*, **33**: 1092, 1957.
7. MORTELL, E. J.: *J. Clin. Endocrinol.*, **6**: 266, 1946.
8. ROBINSON, K. C., KALLBERG, M. H. AND CROWLEY, M. F.: *Brit. M. J.*, **2**: 1203, 1954.
9. MACGREGOR, M. E. AND WHITEHEAD, T. P.: *Arch. Dis. Childhood*, **29**: 398, 1954.
10. ZABRISKIE, J. AND REISMAN, M.: *J. Pediat.*, **52**: 158, 1958.
11. FALLS, H. F.: Skeletal system, including joints, *In*: Clinical genetics, edited by A. Sorsby, Butterworth & Co., Ltd., London, 1953, p. 236.
12. BOWERS, D.: *Ann. Int. Med.*, **51**: 1049, 1959.
13. BRAILSFORD, J. F.: *Brit. J. Radiol.*, **18**: 167, 1945.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

It is a well-recognized fact that men, prejudiced by the teaching of former generations, are often blind to facts which may directly come under their own observation. For example, we find a surgeon who visited Lister's wards in the autumn of 1873 writing his impressions to the *Lancet*, and saying, "I left his wards, as any man who conscientiously desired to find out and uphold the truth must have done in my place, with the last remnant of my belief in Professor Lister dissipated to the winds." There is a warning here to those who would commit their views too hurriedly to writing; they may find, as many of Lister's hostile critics have done, that they have placed on record observations which reflect little credit on their acumen and sagacity.—A. Primrose: Address in Surgery to the 44th Annual Meeting of the Canadian Medical Association, *Canad. M. A. J.*, 1: 601, July 1911.