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Probable Autosomal Recessive Inheritance in a Family with Albright's Hereditary Osteodystrophy and an Evaluation of the Genetics of the Disorder

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INTRODUCTION

Albright's hereditary osteodystrophy exists in two related metabolic forms uninformatively called pseudohypoparathyroidism and pseudo-pseudohypoparathyroidism for the hypocalcemic and normocalcemic states, respectively [1]. They share in common the variably expressed features of short stature, round face, skeletal abnormalities of the hands and feet, and an increased incidence of mild mental retardation [1]. The original hypothesis of Albright and associates that the hypocalcemia is due to an end-organ unresponsiveness to the action of parathyroid hormone (PTH) [2] has been confirmed by the criteria of phosphate excretion [3] and, more recently, increased adenosine 3′,5′-monophosphate (c-AMP) excretion [4] after administration of the bovine hormone. The latter appears to be the initial detectable metabolic response to PTH administration, and lack of augmented excretion of c-AMP after PTH administration is now considered the definitive diagnostic test of the condition [1].

The disease is widely felt to be inherited by a sex-linked dominant mechanism [5, 6]. However, reports of unequivocal male-to-male transmission in families with ectopic calcification or hypocalcemia are incompatible with this formulation [7, 8], and at least two authors cogently dispute the hypothesis [8, 9]. Clinical details of two other instances of reported male-to-male transmission [9, 10] are insufficient to distinguish these families from those with type E brachydactyly. Although families with only siblings affected have been reported, often with adequate examination of the apparently unaffected parents, an autosomal recessive mechanism has never been postulated. The situation is complicated further by the fact that in few of the reported cases was c-AMP excretion measured and the phosphate excretion studies are thought to be less easily interpretable [1].

In this paper, we wish to report on two siblings with the characteristic features of the hypocalcemic form of Albright's hereditary osteodystrophy, in one of whom

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c-AMP excretion in response to PTH was measured and found to be grossly reduced and whose parents showed no biochemical or phenotypical evidence of the disease. An autosomal recessive mode of inheritance seems likely in this case.

CASE REPORTS

Case 1

The pedigree is shown in figure 1. The propositus was first seen at age 6¾ years for evaluation of a mild delay in motor skills and low concentrations of calcium and thy-

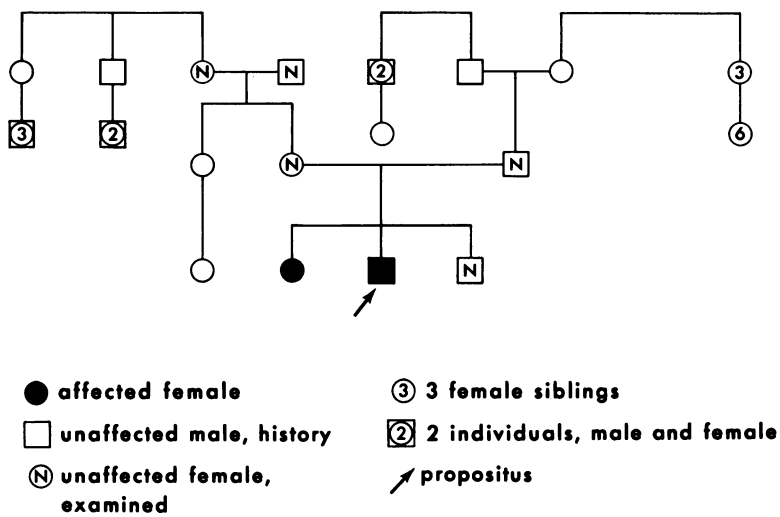

FIG. 1.—C family pedigree

roxine (T_4) in the serum. These results and subsequent determinations are reported in table 1. Hypocalcemia and hypothyroidism with increased thyroid-stimulating hormone (TSH) are noted. The patient was in the sixteenth percentile for height and ninetieth percentile for weight. He had a pudgy appearance, rounded facies (fig. 2), generalized shortening of all metacarpals and genu valgum. No soft tissue calcifications were palpable. Gross neurologic examination and mental capacity appeared normal for age. School per-

TABLE 1

INITIAL LABORATORY DATA

CASE	CALCIUM (meq/liter)	PHOSPHORUS (meq/liter)	ALKALINE PHOSPHATASE (KAU)	T_4 MURPHY-PATTEE (mg/100 ml)	TSH (μU/ml)	UPTAKE (%) 6 hr	UPTAKE (%) 24 hr
1	3.6	4.5	20	3.0	27	5	8
	3.5	4.4	...	4.8	20	...	...
2	3.5	3.3	18	4.8	11	...	...
	3.5	3.4	...	...	20	...	...
Normal sibling ..	5.0	2.5	...	7.6	...	...	...

NOTE.—Normal values: calcium, 4.5–5.4 meq/liter; phosphorus, 1.8–3.0 meq/liter; alkaline phosphatase, 12–50 KAU in children; T_4, 5–11 mg/100 ml in children; TSH, <9 μU/ml.

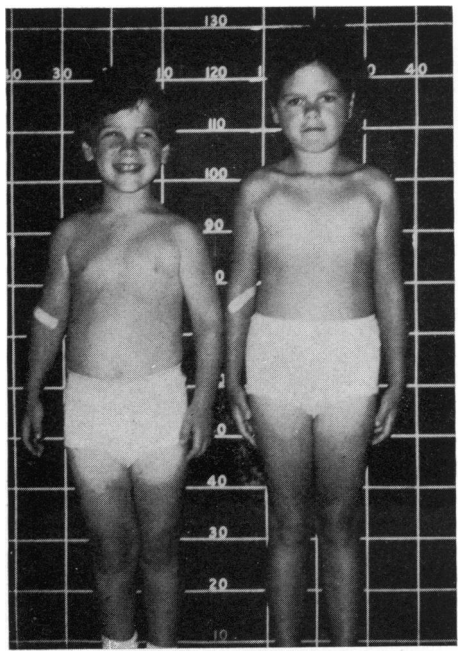

FIG. 2.—Photograph of propositus and his affected sister prior to therapy

formance was poor but at grade level. Roentgenographic studies showed scattered soft tissue calcifications in the hands and feet and marked shortening of all metacarpal, metatarsal, and phalangeal structures with selective shortening of the fourth metatarsal. The karyotype was 46,XY.

Case 2

The 9¾-year-old sister of the propositus was seen when a family history revealed that she had noticably shortened fourth metatarsals. She was in the tenth percentile for height and twentieth for weight and had no systemic complaints. Except for shortened metacarpals and extremely short metatarsals (fig. 3), her physical examination, including

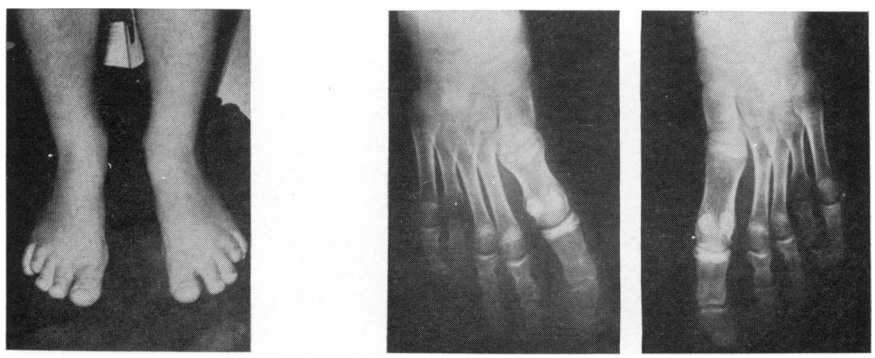

FIG. 3.—Photograph and X-ray views of the feet of case 2 demonstrating the marked shortening of the fourth metatarsal and toe.

neurologic status, showed no abnormalities. School performance was at grade level. She, too, had hypocalcemia and borderline thyroid function (table 1). The karyotype was 46,XX.

METABOLIC STUDIES AND CLINICAL COURSE

Following a period on a low phosphorus diet (200 mg/day for 5 days), urinary phosphorus and c-AMP excretion in the propositus were determined in response to intravenous PTH. The procedure was similar to that suggested by Bethune et al. [11]. The patient was tested reclining in the afternoon. After collection of urine during three 1-hr control periods, 150 USP units of purified PTH was infused in 25 ml of 0.9% NaCl containing 0.5% human serum albumin over a period of 10 min. Urine was collected during three subsequent 1-hr periods. Results of the test are listed in table 2. The ratio of the highest postinfusion excretion rate for phosphorus

TABLE 2

URINARY EXCRETION OF c-AMP AND PHOSPHORUS IN RESPONSE TO PTH

CASE	CONTROL PERIODS			AFTER PTH INFUSION		
	1 hr	2 hr	3 hr	1 hr	2 hr	3 hr
Case 1:						
c-AMP* (nmoles/min)	0.6	1.5	1.4	1.3	1.0	1.8
Phosphorus (mg/hr)	5.6	10.5	12.5	16.5	13.8	10.3
Control patient:						
c-AMP* (nmoles/min)	0.9	4.0	4.0	462	6.0	8.3

* Measured by the radioimmunoassay method of Steiner et al. [12].

(16.5 mg) to the average preinfusion rate (9.5 mg) was 1.8. This low ratio indicates a poor response of renal excretion of phosphorus to PTH. A ratio of greater than five is normally achieved [11]. Urinary c-AMP excretion also failed to increase in the patient, although a marked increase was observed in a control subject. The response in the normal subject to PTH infusion is similar to that reported by others [4].

Following these initial studies, the proband and his sister were treated with 0.2 mg dihydrotachysterol and Euthroid no. 3 ® (a combined thyroxine-triiodothyronine preparation) daily. The propositus's serum calcium concentration stabilized at or near 4.5 meq/liter and his serum TSH became suppressed to undetectable levels. He has grown 8 cm in 1 year to the fortieth percentile and gained 1 kg, resulting in a taller, thinner appearance. His sister also maintains calcium and T_4 levels within the normal range on this regimen. Her growth increase has been less dramatic, and she remains below the twenty-fifth percentile for height.

The C family pedigree is shown in figure 1. A 2-year-old male sibling was examined and found to be in the sixtieth percentile for height and weight. No bony or soft tissue stigmata of Albright's hereditary osteodystrophy were seen, and serum calcium, phosphorus, and T_4 were all normal.

The parents were carefully examined. They were lean, of average height, had normal hands, feet, and facial appearance, and were dynamic people of above-average intelligence. They were both normocalcemic. The maternal grandparents and siblings were similarly normal and no stigmata of this syndrome were said to be present in any members of the paternal family. Consanguinity was denied and the ethnic and geographic backgrounds of the parents were sufficiently diverse to confirm this. Twenty-five genetic markers including blood groups, serum proteins, red cell enzymes, and HL-A antigens were studied in the parents and the two affected siblings and did not exclude correct paternity. Using the method of Stern [13], the likelihood of incorrect paternity for the boy was less than 0.28% and for the girl, less than 0.31%. The likelihood of incorrect paternity for both is 0.087%, or substantially nil.

DISCUSSION

Both of these patients appear to fulfill many of the major criteria for the hypocalcemic form of Albright's hereditary osteodystrophy. The serum calcium was consistently reduced in both, and soft tissue calcifications were demonstrable although no gross symptoms due to hypocalcemia were present. Metacarpal shortening with small spadelike hands was present, as were equivalent changes in the feet (fig. 3). The face was found, the neck short, and the short, stocky build typical of the syndrome was present in both (fig. 2). Their height was at the lower end of the normal distribution in contrast to that of an apparently normal sibling in the sixtieth percentile. The patients were quiet and shy with a borderline school performance, but true retardation could not be documented. The greatly diminished response of case 1 to PTH infusion, as compared with a normal control (table 1), is characteristic of this syndrome and is considered to be diagnostic of it [1]. Borderline or abnormally low thyroid function has been described in other patients with this disorder [14, 15]. The mechanisms appear to vary and in some may represent a defect analagous to the failure to respond to PTH, that is, failure of the adenyl cyclase system to respond normally to TSH in the thyroid gland or perhaps to thyrotropin-releasing hormone in the anterior pituitary [15]. In others, the disorder appears to be one of primary thyroidal failure. The degree to which the borderline low thyroid function was functionally significant in these patients is unclear because both thyroid and dihydrotachysterol therapy were started concomitantly. Therefore, the increase in growth rate exhibited by the propositus may be attributed to either. However, similar growth responses following normalization of calcium levels in the serum have not been clearly documented.

The findings in this family are most compatible with inheritance in an autosomal recessive manner. Other mechanisms are, of course, possible. A sex-linked dominant or autosomal dominant mechanism with wide differences in penetrance and expressivity seems unlikely in view of the lack of precedence in this disorder and the full manifestation of most of the usual symptoms in the children. A dominant disease resulting from a somatic gonadal mutation is also conceivable, but this has never been unambiguously demonstrated in man and must be considered unlikely.

The most widely accepted mode of inheritance for this syndrome is sex-linked dominant, a hypothesis based partly on the absence of male-to-male transmission. However, two families with male-to-male transmission and autosomal dominant inheritance have been reported and can no longer be discounted [7, 8]; thus at least one form of this syndrome must be inherited in this manner. Reports in these same families of unaffected female offspring of affected males are incompatible with the sex-linked hypothesis. Similarly, our own review of the literature reveals that with the exception of the few specific families noted above, familial cases in which a form of dominant inheritance is postulated lack not only male-to-male transmission but also have few reported cases of affected males with children of either sex. Such an observation must cast doubt on the importance of the relative lack of male-to-male transmission that has been noted.

A second argument for sex-linked inheritance comes from an apparent 2:1 excess of females over males with the syndrome. Spranger [9], however, found a female:male ratio of only 1.2:1 when siblings of propositi were considered, and felt that this ratio was compatible with an autosomal dominant form of inheritance with ascertainment bias in favor of females.

The observation that females seem as seriously or more seriously affected than males [5] is also in conflict with a postulated sex-linked mechanism. Since approximately half of the renal or bone cells in females may most likely be expected to have normal responses to PTH as a consequence of the Lyon effect [16], females would be expected to be less seriously affected and less prone to hypocalcemia than males. Such a hypothesis would not be true if a soluble inhibitor were to be the basis of the syndrome, but this is not considered a serious pathogenic possibility [1].

A review of all cases collected by Mann et al. [5], Spranger and Rohwedder [17], and Spranger [9] demonstrates that many of the reported familial cases occur in siblings alone, often with adequate examination of apparently normal parents. It would appear, then, from our report and others that the syndrome may also be inherited in an autosomal recessive manner and this implies heterogeneity of genetic mechanisms in the etiology of the condition. The arguments summarized above, most of which were originally elucidated by Spranger [9] and Spranger and Rohwedder [17], support the existence of an autosomal dominant form of the syndrome; a sex-linked form may also exist. Although a sex-influenced autosomal dominant mechanism might explain the findings in our family and the preponderance of female cases, the absence of convincing reports of unaffected obligate male carriers (or female carriers) and the relative equality in severity of disease in patients of both sexes make this hypothesis unlikely.

The pathogenesis of Albright's hereditary osteodystrophy is uncertain. Marcus et al. [18] have found that the renal tissue obtained at postmortem from a patient with this syndrome contained normal amounts of PTH-responsive adenyl cyclase, while her sister with the syndrome failed to increase c-AMP excretion after PTH was administered. Similarly, ambiguous data have been obtained by Chase et al. [4] showing a normal c-AMP response in one family member with normocalcemia

and no response in another with hypocalcemia. Since an apparent shift from hypo- to normocalcemia has been shown to occur in the same person [19, 20], a reasonable, though uncertain, conclusion would be that failure of the renal c-AMP response, although genetically conditioned, may be variable for a given gene and possibly within a given individual. Given the complexity of such biological responses and the predictability that at least several steps must mediate this total response, genetic and pathogenic heterogeneity should be a likely rather than a surprising event. It is in this context—of several loci and modes of inheritance, and probably at least several alleles at each—that the heterogeneity of this disease must be viewed. The recognition of heterogeneity is important for the study of the pathogenic mechanisms of the disease as well as for genetic counseling.

SUMMARY

Two siblings with Albright's hereditary osteodystrophy are presented and an autosomal recessive mechanism of inheritance is postulated in this family. Data on the inheritance of this condition are reviewed and appear to cast doubt on the sex-linked dominant mechanism previously postulated as the primary mechanism of inheritance. It appears that autosomal recessive and autosomal dominant inheritance both occur in this condition and, thus, it represents an etiologically heterogeneous entity.

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