Syndrome of the month

Albright's hereditary osteodystrophy

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History and terminology

In 1942 Albright *et al*[1] investigated a patient with seizures, hypocalcaemia, and hyperphosphataemia consistent with a diagnosis of hypoparathyroidism. Unexpectedly, repeated injections of bovine parathyroid extract failed to alter the serum calcium or phosphate levels. They concluded the patient was resistant to parathyroid hormone (PTH) rather than deficient and coined the term pseudohypoparathyroidism (PHP). Additional features, (a short stocky build, round face, cutaneous ossification, and metacarpophalangeal abnormalities) were sufficiently distinctive for two unrelated but phenotypically similar patients with hypocalcaemia to be recalled and shown to have PTH resistance. This physical appearance is known as Albright's hereditary osteodystrophy (AHO).

A decade later, Albright *et al*[2] described a further patient with typical features of AHO but normal serum calcium and phosphate. Recognising the phenotypic similarities but absence of PTH resistance, he named this disorder pseudopseudohypoparathyroidism (PPHP).

Subsequent reports of families where both conditions were segregating suggested an aetiological link.

Aetiology

PTH, like TSH and several other hormones,[3] exerts its effects by stimulating adenylyl cyclase to produce the intracellular second messenger cAMP. Their receptors are coupled to adenylyl cyclase by a signal transducing protein known as Gs, one of a large family of heterotrimeric GTP binding G proteins.[4-6] Gs comprises an α, β, and γ subunit (fig 1). The α subunit appears to determine both the receptor and effector specificity.

In 1980 two groups showed that Gsα activity in erythrocyte membranes from patients with PHP was reduced to 50% of normal controls.[7,8] Similar reductions have been found in membranes of platelets,[9] fibroblasts,[10] and renal cortex[11] from patients with PHP. Intriguingly, equivalent Gsα reductions have been found in membranes from patients with PPHP, despite their lack of hormone resistance.[12]

Diagnosis and classification

A diagnosis of PHP may be inferred in a patient who has hypocalcaemia, hyperphosphataemia,

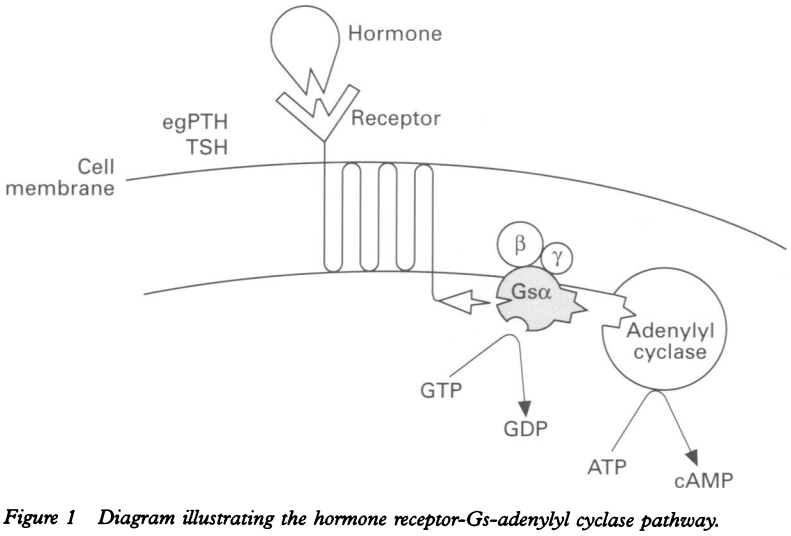

Figure 1 Diagram illustrating the hormone receptor-Gs-adenylyl cyclase pathway.

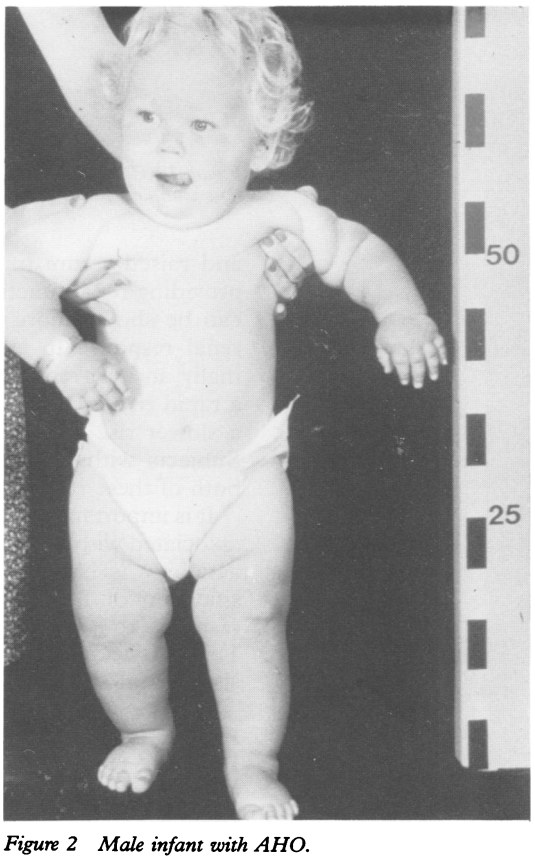

Figure 2 Male infant with AHO.

Table 1 Classification of pseudohypoparathyroidism

Type	*Response to PTH*	*Phenotype*	*Multiple hormone resistance*	*Gsα levels (% controls)*	*Aetiology*
PHP Ia	Blunted cAMP Blunted Pi	AHO	Frequent	50	Deactivating Gsα gene mutation
PHP Ib	Blunted cAMP Blunted Pi	No AHO	No	100	? PTH receptor
PHP Ic	Blunted cAMP Blunted Pi	AHO	Frequent	100	? Defective adenylyl cyclase
PHP II	Normal cAMP Blunted Pi	No AHO	No	100	? Distal to adenylyl cyclase ?phospholipase C pathway[17]
PPHP	Normal cAMP Normal Pi	AHO	No	50	Deactivating Gsα gene mutation

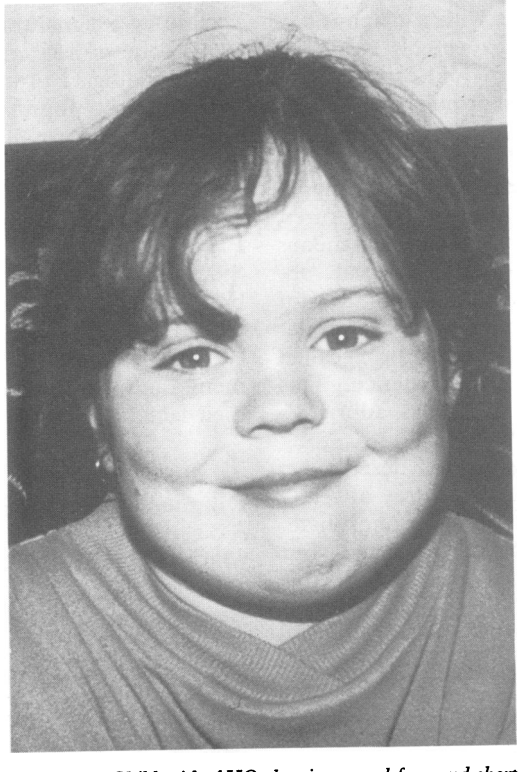

Figure 3 Child with AHO showing round face and short nose with low, flattened nasal bridge.

and raised serum immunoactive PTH levels, providing renal function is normal. Resistance can be shown more directly by assessing the renal response to exogenous PTH.[13-15] Normally an intravenous bolus of PTH produces a rapid rise in plasma and urinary cAMP with a slower rise in urinary phosphate excretion. Subjects with PHP have blunting of one or both of these responses (table 1).

It is important to note that PHP is not always associated with AHO and in such instances the aetiology is likely to be different. The classification of PHP is therefore based on the response to PTH testing and Gsα levels (table 1).[16-18] The majority of those with PTH resistance and AHO have PHP Ia.

Persons with PPHP have, in addition to the AHO phenotype, a normal renal response to PTH but reduced levels of Gsα (table 1). Use of the term PPHP to denote any person with AHO who is normocalcaemic is unhelpful since periods of normocalcaemia are frequent in PHP, even when resistance to PTH has been established through PTH infusion testing.

Clinical features

Typical patients with AHO (figs 2 and 3) have a pleasant, affable nature, short, stocky build, round face with a low, flat nasal bridge, short neck, ectopic ossification, brachymetaphalangism, and developmental delay, with or without endocrine abnormalities, and these subjects pose little diagnostic difficulty. However, aspects of the phenotype may vary considerably from one patient to another.

GENERAL APPEARANCE

Fitch[19] noted short stature in 39% of patients with AHO below the age of 18 years and 62% of adults. These findings and longitudinal studies[20,21] suggest that advanced skeletal maturation is a contributing factor. There is typically a shortening of the extremities.[22,23] Occipitofrontal circumference is generally within the normal range but macrocephaly has been described.[19] Obesity is usual and often arises in early childhood.[19]

NEUROMUSCULAR

Mental retardation has been reported in 52/66 (70%) hypocalcaemic and 19/64 (30%) normocalcaemic patients with AHO.[19] In PHP Ia, mild to moderate mental retardation occurred in 9/14 (64%) patients.[24] There appeared to be a strong correlation with reduced Gsα activity since no patients with PHP Ib had mental retardation in spite of equivalent serum calcium and phosphate abnormalities. While untreated hypothyroidism may contribute to the degree

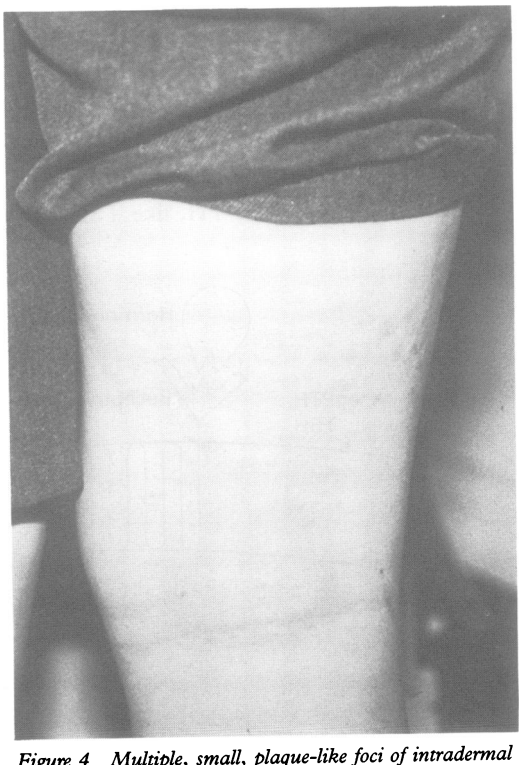

Figure 4 Multiple, small, plaque-like foci of intradermal ossification on the dorsal aspect of the thigh in a child with AHO.

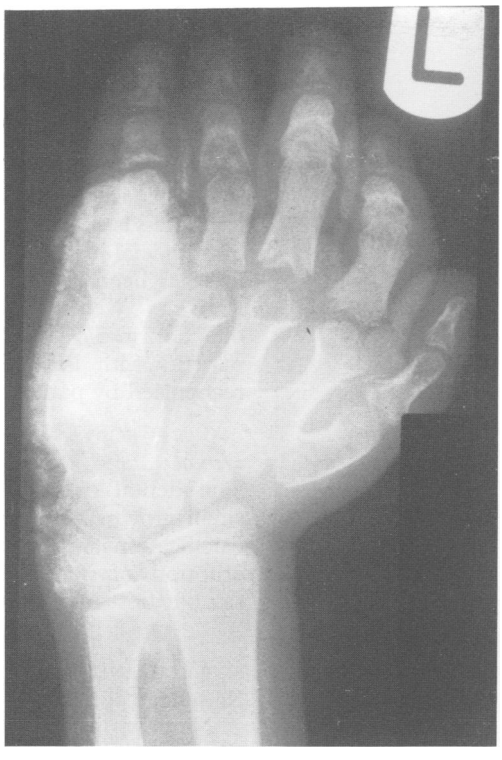

Figure 5 Plain radiograph of hand of a 4·7 year old female with AHO showing a large focus of subcutaneous ossification, brachymetaphalangism (involving all the metacarpals), phalangeal shortening, cone shaped epiphyses, and advanced bone age.

of mental retardation, it is unlikely to be the primary cause.[18 24]

Our own observations confirm that mental retardation in AHO may range from moderately severe delay to entirely normal educational ability, but is in general mild. Of 16 adults, many have needed remedial help or special schooling but 15/16 (94%) have subsequently been able to live independently, remain in employment and, care for families of their own.

Seizures, usually grand mal, occur in AHO and may be independent of hypocalcaemia. Tetany and largyngeal stridor[1] may occur secondary to hypocalcaemia and the latter, if unrecognised, may result in unnecessary tracheostomy.

ECTOPIC CALCIFICATION

Spranger[25] noted cutaneous calcification in 42% of reported patients with PHP and 27% with normocalaemic AHO, intracranial calcification occurring in 33% and 4% respectively.

Cutaneous calcification may be intradermal or subcutaneous, is frequently ossified,[1 26–28] and has been noted within days of birth.[23] It is usually painless and often appears as multiple small superficial plaques (fig 4), easier to feel than see, with a predilection for the scalp, hands and feet, periarticular regions, abdomen, and chest wall. Larger lumps may occur, occasionally disrupting underlying structures (fig 5).

Intracranial calcification commonly involves the basal ganglia but may involve other structures including the dentate nucleus,[29] falx cerebrum,[1] dura, cerebral cortex, and cerebellum.[30] Calcification may occur at other sites including the sclera, choroid,[31] and cardiac ventricular septum.[32]

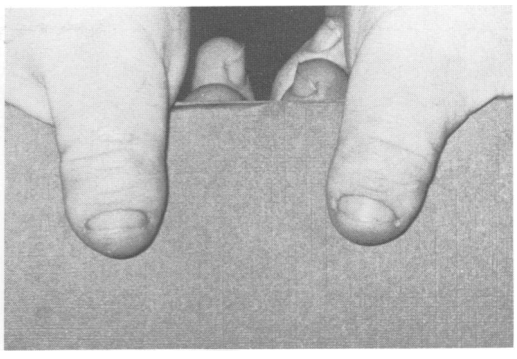

Figure 6 Short, broad thumb nails of an adult with AHO.

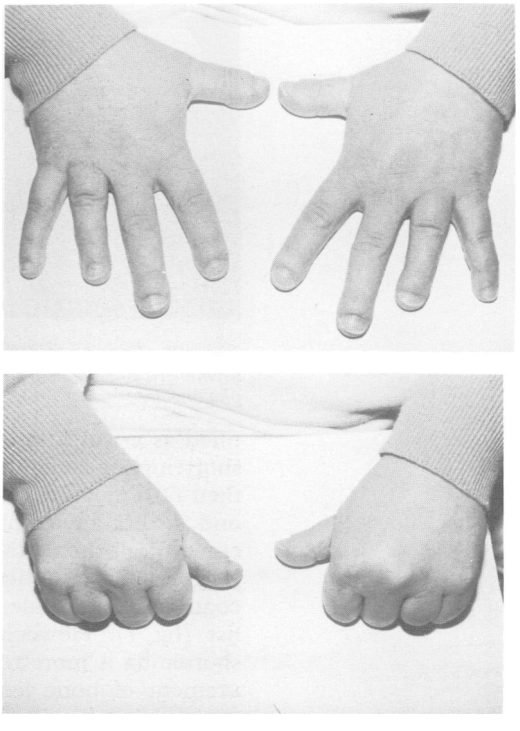

Figure 7 Hands of an adult with AHO showing marked shortening of the fourth metacarpal and distal phalanges with knuckle dimples in the clenched fists.

Soft tissue ossification appears to arise by a mechanism independent of serum calcium and phosphate levels since it occurs in PPHP, frequently precedes the biochemical abnormalities in PHP, and is rare in idiopathic hypoparathyroidism. Excision has been recommended for potentially troublesome or disfiguring foci[19 28] and, unlike myositis ossificans, surgery does not appear to aggravate the condition (Wilson and Trembath, unpublished observations).[33] In contrast intracranial calcification is probably related to altered calcium/phosphate ratio.

BRACHYMETAPHALANGISM

Hand abnormalities in the PHP and PPHP forms of AHO appear indistinguishable,[34] involve both the phalanges and metacarpals, and may be asymmetrical. Shortening of the distal phalanx of the thumb, estimated to occur in 75% of AHO patients,[34] is as frequent as metacarpal shortening. This manifests as a short broad thumb nail (fig 6) which may be quan-

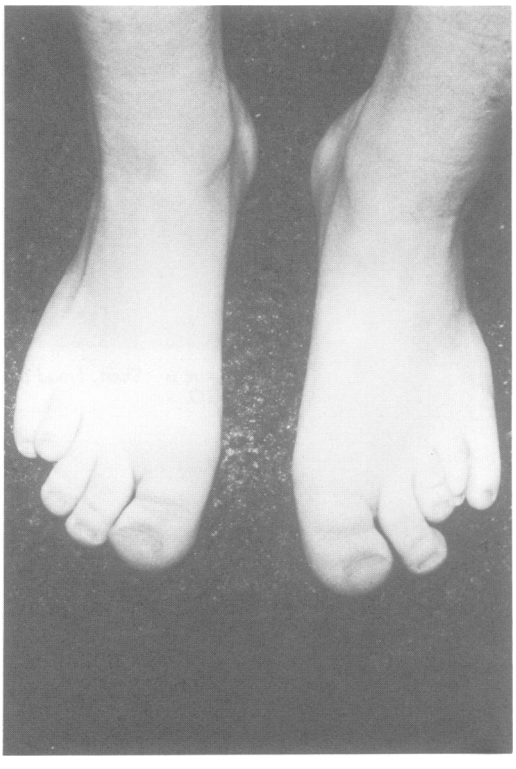

Figure 8 Feet of a child with AHO showing asymmetrical metatarsal shortening and shortened distal phalanges.

tified as a width to length ratio.[35] Metacarpal shortening most commonly involves the fourth then fifth metacarpals and least often the second,[2334] but any combination or indeed shortening of all the metacarpals may be observed (figs 5 and 7). When marked it may be recognised by knuckle dimples in the clenched fist (fig 7). However, subtle or generalised shortening is more reliably detected by measurement of bone lengths on *x* ray and metacarpal pattern profiles.[34] It is important to note that the characteristic hand changes evolve with age and may not be apparent until at least 4 years.

Similar abnormalities of the feet (fig 8) occur in at least 70% of persons with AHO, shortening of the fourth then third metatarsals occurring most frequently.[29] Phalangeal shortening also occurs but is more difficult to evaluate owing to the wide range of normal variation.

OTHER FEATURES

Eye

Cataracts and lenticular opacities have been described in PHP probably related to the hypocalcaemia/hyperphosphataemia.[25] Strabismus occurred in 10% in one series.[36] Scleral and choroidal calcification have been observed.[31]

Hearing/olfaction

In our experience a history of glue ear requiring grommets is common in AHO perhaps because of midfacial hypoplasia. Sensorineural hearing loss has been identifed in some patients with PHP Ia.[37] Weinstock *et al*[38] reported impaired olfaction in 5/5 patients with PHP Ia but 0/7 patients with PHP Ib; however, it is rarely recognised by patients.

Dental

The dental manifestations in PHP include small crowns, thin hypoplastic enamel, pulp calcifications, widened root canals, and delayed eruption of permanent teeth,[2939–41] and resemble those of idiopathic hypoparathyroidism.

SKELETAL AND RADIOLOGICAL FEATURES

Radiological findings are summarised in table 2. Notably, in persons with PHP Ia, evidence of osteomalacia or rickets may arise owing to low levels of 1,25 vitamin D, secondary to renal PTH resistance. Conversely, findings of generalised osteoporosis and occasionally osteitis fibrosa cystica[2942] suggest some preservation of the skeletal remodelling response to the raised levels of circulating PTH.[184243]

In both forms of AHO, bone age measured by the carpal bone (CB) score or the radius-ulna-short (RUS) bone score is generally advanced,[192129] the discrepancy with chronological age being greatest for the RUS score.[21] The cone shaped, absent, and prematurely fused epiphyses in the hands and feet are thought to contribute to metacarpal and phalangeal shortening and, combined with decreased longitudinal growth, to explain the increasing prominence of these bony changes with age.

Exostoses are frequent in AHO but are not usually numerous and are generally distinguishable radiologically from multiple familial exostoses.[29]

Endocrinological features

Resistance to hormones other than PTH occurs in PHP Ia with effects on the thyroid and gonadal axes being of clinical importance.

THYROID

Hypothyroidism secondary to TSH resistance is common in PHP Ia and has been the presenting feature in some neonates.[4445] In a series of 13 persons with PHP Ia,[46] 69% were found to have reduced T4, 69% reduced T3, 85% raised TSH, and 92% had an exaggerated TSH response to TRH. Thyroid function should be tested regularly.

GONADAL

Gonadal dysfunction, particularly menstrual irregularity, has been described, probably sec-

Table 2 Common radiological findings in AHO

General	*Hands/feet*	*Limbs*	*Axial*	*Skull*
Ectopic calcification/ ossification	Metacarpal and phalangeal shortening	Shortened ulna	Caudal narrowing of lumbar interpedicular distances	Thickened calvarium with widened diploe
Advanced bone age	Cone shaped, absent, prematurely fused epiphyses	Radial bowing		Hyperostosis frontalis interna
Osteoporosis		Tibial bowing		Intracranial calcification
Exostoses	Metacarpal thickening and loss of diaphyseal constriction	Coxa vara		Retained teeth
Osteomalacia/ rickets		Coxa valga		Pulp calcifications
Osteitis fibrosa cystica				

ondary to gonadotrophin resistance.[40 47 48] In practice, investigation is probably only merited if problems arise.

GROWTH HORMONE

Growth hormone (GH) secretion and GH treatment for short stature in AHO has not been widely evaluated, possibly because short stature is also a feature of the hormone responsive form (PPHP).

Genetics

The human Gsα gene spanning 20kb and 13 exons was cloned in 1988.[49] It has been localised to chromosome 20q13[50 51] and is present in single copy per haploid genome. Heterozygous loss of function mutations of the Gsα gene have been found both in persons with PHP Ia and PPHP. These have predominantly been single base changes[52–55] and small deletions[53 54 56] with a 43bp deletion being the largest to date.[57] So far mutations have been unique to each family and there are no obvious mutation hot spots. Furthermore in five reported families, related persons with PHP Ia and PPHP have been found to have the same Gsα mutation.[52–54] Additional factors therefore appear to influence the phenotype resulting from such Gsα gene mutations and one of these may be the parental origin.

An excess of maternal transmissions has long been recognised in AHO and until recently X linked dominant inheritance was commonly counselled. In a recent review of reported familial cases, offspring with PHP I were found to result exclusively from maternal transmission and the few offspring with PPHP from paternal transmission.[58] We have noted a concordance of phenotype in nine affected sibs from four different families and in one family have observed a switch in phenotype from PPHP in a female with a paternally derived Gsα abnormality to PHP Ia in her own offspring[55]

This suggests that the Gsα gene may be subject to a parent of origin effect, perhaps through imprinting. Localisation of GNAS, the mouse homologue of Gsα, to an imprinted region of distal mouse chromosome 2 provides some support for this theory.[59 60] However, since equivalent reductions in Gsα bioactivity have been found in PHP Ia and PPHP in all membranes so far tested, imprinting would necessarily be operating at a tissue or even cell specific level.[55]

Differential diagnosis

Confusion often arises between McCune-Albright syndrome and AHO although the two are clinically entirely distinct. Remarkably, both result from mutations in the Gsα gene; however, in the McCune-Albright syndrome these are gain of function mutations and occur on a somatic mosaic basis.[61]

There is considerable phenotypic overlap between PPHP and acrodysostosis[62 63] since short stature, brachymetaphalangism, advanced bone age, mental retardation, and many radiological features are common to both. The generalised metacarpal and phalangeal shortening characteristic of acrodysostosis has also been observed in confirmed cases of AHO (Wilson and Trembath, unpublished observations).[64] Cutaneous ossification does not occur in acrodysostosis but is not universal in PPHP. Pronounced nasal hypoplasia is considered a distinguishing feature of acrodysostosis but has been observed in patients with PHP Ia.[64]

Similar overlap occurs with the isolated brachydactyly syndromes E and D[65] since they may be radiologically indistinguishable from AHO[34] and have been observed to segregate in families where AHO is segregating.[66] Acrodysostosis and the brachydactylies may represent poles of the phenotypic spectrum of AHO and Gsα evaluation will help to resolve this issue.

Other syndromes including Turner's syndrome and multiple familial exostoses are associated with short stature and metacarpal shortening but rarely cause diagnostic confusion.

The soft tissue ossification of myositis ossificans is distinguishable by its location in muscle and frequently painful, disabling nature.[67] Furthermore, the characteristic single phalanx, or phalangeal fusion of the big toe and shortening of the first metacarpal or proximal phalanx of the thumb in myositis ossificans contrasts with the pattern of shortening in AHO.

AHO has been observed in association with chromosomal abnormalities, specifically 15q[68] and 2q[69] deletions, but coincidental pathology was not excluded by Gsα measurement.

Other forms of PHP are distinguishable on endocrine and metabolic grounds (table 1).

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