Management of pseudohypoparathyroidism

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Purpose of review
This review is timely given the 2018 publication of the first international Consensus Statement for the diagnosis and management of pseudohypoparathyroidism (PHP) and related disorders. The purpose of this review is to provide the knowledge needed to recognize and manage PHP1A, pseudopseudohypoparathyroidism (PPHP) and PHP1B – the most common of the subtypes – with an overview of the entire spectrum and to provide a concise summary of management for clinical use. This review will draw from recent literature as well as personal experience in evaluating hundreds of children and adults with PHP.

Recent findings
Progress is continually being made in understanding the mechanisms underlying the PHP spectrum. Every year, through clinical and laboratory studies, the phenotypes are elucidated in more detail, as are clinical issues such as short stature, brachydactyly, subcutaneous ossifications, cognitive/behavioural impairments, obesity and metabolic disturbances. Headed by a European PHP consortium, experts worldwide published the first international Consensus that provides detailed guidance in a systematic manner and will lead to exponential progress in understanding and managing these disorders.

Summary
As more knowledge is gained from clinical and laboratory investigations, the mechanisms underlying the abnormalities associated with PHP are being uncovered as are improvements in management.

Keywords
Albright hereditary osteodystrophy, GNAS, pseudohypoparathyroidism, pseudopseudohypoparathyroidism

INTRODUCTION
In 1942, Fuller Albright et al. [1] described a disorder characterized by end-organ resistance to parathyroid hormone (PTH) resulting in increased serum PTH levels, hypocalcaemia and hyperphosphataemia. The patients lacked the appropriate response to administration of PTH and had blunted urinary cAMP and phosphate excretion. The condition was named ‘pseudohypoparathyroidism’ (PHP) given that the PTH was elevated in the face of low calcium and high phosphorous levels [1]. These patients had specific somatic and developmental abnormalities such as a round facies with a ‘short, thickset figure’, heterotopic subcutaneous ossifications (SCOs), brachydactyly and cognitive impairment [1] (for review, [2,3]). This was later to be termed PHP type 1A (PHP1A). Approximately a decade later, Albright et al. [4] also identified a patient who had many of these same physical features but normal calcium, phosphorus and PTH levels as well as a normal phosphaturic response to PTH; this was named pseudopseudohypoparathyroidism (PPHP). The physical phenotype for both PHP1A and PPHP was termed Albright hereditary osteodystrophy (AHO).

AHO is a disorder caused by heterozygous inactivating mutations affecting exons 1–13 of GNAS, the gene encoding the α-chain of the stimulatory G protein, Gαs, which couples receptors for many hormones and neurotransmitters to activate adenylyl cyclase. GNAS is a complex locus [2,3] that encodes not only Gαs, with mutations causing AHO found in

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Curr Opin Pediatr 2019, 31:537–549
DOI:10.1097/MOP.0000000000000783

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KEY POINTS

- The first international Consensus Statement for the diagnosis and management of PHP and related disorders published in 2018 is a milestone in the field and provides a comprehensive description of the underlying mechanisms and clinical management for these overlapping conditions.

- As more patients have been identified and treated, it has become clear that the classic descriptions of the PHP disorders are evolving, and hence a detailed, up-to-date understanding of the phenotypes is critical both to diagnosis and management; a recent example of the identification of obesity in infancy in PHP1B, which can be an early indicator for further diagnostic testing and appropriate clinical management.

- Growth hormone testing is standard of care for patients with PHP1A to identify those with GH deficiency, which in combination with the known premature epiphyseal fusion and absent pubertal growth spurt, typically results in short stature in adults; because children with PHP1A are typically not short, it is important not to delay GH testing until growth has decelerated so that the benefits of GH treatment can be maximized.

- Careful physical examinations, such as examination of the hands/feet for brachydactyly or the skin for subcutaneous ossifications, are critical to diagnosis, particularly to identify PPHP patients in order to provide early genetic counselling and to identify PHP1A infants who have been misdiagnosed with congenital hypothyroidism.

- The medical, developmental and cognitive/behavioural issues that can occur in PHP should involve early intervention as well as long-term management by a medical team that is knowledgeable about these disorders and able to provide the necessary support and advocacy for the patients and their families.

Patients with PHP1A have GNAS mutations on the paternally inherited allele and have the AHO phenotype alone without hormonal resistance or the severe obesity. The identification of the difference in the obesity phenotype between PHP1A and PPHP raised the possibility that paternal imprinting in the hypothalamus may be the cause [8], given that the melanocortin 4 receptor (MC4R) is Gs-coupled, and this difference in phenotype was recently found to be due to imprinting in the dorsomedial hypothalamus, specifically the MC4R-expressing cells, based on extensive work on mouse models [9,10]. Thus, women affected with AHO have children with PHP1A affected by hormonal resistance and obesity, whereas men with AHO have children with PPHP without hormonal resistance and obesity [2,3,8,11].

Although the phenotype of a patient with AHO can be explained by the parental mode of transmission of the GNAS mutant allele, spontaneous mutations can also occur. In addition, abnormalities in imprinting due to mutations that affect methylation patterns typically cause a condition termed PHP1B (described below). PHP1C is also within this group of disorders but difficult to prove, as it presents in the same manner as PHP1A; it is due to mutations that impair receptor coupling activity of Ga3, but not its basal activity.

Other conditions in the PHP spectrum of disorders are described in Table 1 including progressive osseous heteroplasia (POH) and the very rare PHP1A/POH combination [12,13]. When patients have a similar phenotype to PHP1A but do not have a mutation in GNAS, other related disorders need to be considered. The acrodyostosis syndromes have similarities to AHO but a more severe skeletal phenotype including striking midface/nasal hypoplasia; these syndromes can also involve resistance to multiple G protein coupled hormones. The genes involved in these disorders (Table 1) are downstream from GNAS in the cAMP pathway. Thus, all of the PHP and related disorders represent a spectrum with many similarities, all within this one pathway [14].

PHP is rare, and the prevalence is not truly known (estimate for Denmark: 1.1 per 100 000, 2016) [15]; however, the prevalence may be closer to 1:20 000 in the United States (unpublished). PPHP is especially likely to be more common than realized, as patients with this disorder often go unrecognized. In 2016, the European consortium for PHP proposed a methodological approach to classification based on ‘inactivating PTH/PTHrP signaling disorders’ in order to base the disorders on underlying mechanisms rather than phenotype [16]. This led to the European consortium for PHP to assemble experts from around the world to restructure characterization based on molecular...
Consensus is a true milestone for the field of PHP and related disorders. Published in 2018, this consensus Statement on the diagnosis and management causes and to develop the first international Consensus Statement on the diagnosis and management of PHP and related disorders. Published in 2018, this Consensus is a true milestone for the field [17**].

The goal of this brief review is to provide the background to understand the most common PHP disorders within the framework of recent advances, as well as their management. A condensed summary of the pertinent details necessary for management of PHP1A, PPHP and PHP1B has been formulated into Table 2 to serve as an easy-to-use tool for clinical care. To understand the reasons behind the management detailed in Table 2, the basis of the similarities and differences between these disorders is explained in this review. For the most comprehensive set of guidelines for management of PHP and related disorders, the 2018 international Consensus Statement is recommended.

**PSEUDOHYPOPARATHYROIDISM TYPE 1A AND PSEUDOPSEUDOHYPOPARATHYROIDISM**

In tissues in which imprinting of GNAS does not play a prominent role, the phenotypic consequences of heterozygous loss of GNAS can be similar between the disorders, whereas in tissues in which imprinting does play a significant role, the clinical phenotypes can be very different depending on the parent-of-origin of the mutant GNAS allele.

| Inheritance | PHP1A | PPHP | PHP1B | Osteoma cutis | POH | ‘AHO/PHP1A-like’ |
|------------|-------|------|-------|---------------|-----|-----------------|
| Loss of maternal GNAS methylation imprints, deletions in GNAS or STX16, inversions of GNAS regions; autosomal dominant and sporadic forms | Loss of maternal GNAS methylation imprints, deletions in GNAS or STX16, inversions of GNAS regions; autosomal dominant and sporadic forms | Loss of maternal GNAS methylation imprints, deletions in GNAS or STX16, inversions of GNAS regions; autosomal dominant and sporadic forms | Loss of maternal GNAS methylation imprints, deletions in GNAS or STX16, inversions of GNAS regions; autosomal dominant and sporadic forms | Loss of maternal GNAS methylation imprints, deletions in GNAS or STX16, inversions of GNAS regions; autosomal dominant and sporadic forms | Loss of maternal GNAS methylation imprints, deletions in GNAS or STX16, inversions of GNAS regions; autosomal dominant and sporadic forms | Loss of maternal GNAS methylation imprints, deletions in GNAS or STX16, inversions of GNAS regions; autosomal dominant and sporadic forms |
| Rarely due to GNAS imprinting defect | Rarely due to GNAS imprinting defect | Rarely due to GNAS imprinting defect | Rarely due to GNAS imprinting defect | Rarely due to GNAS imprinting defect | Rarely due to GNAS imprinting defect | Rarely due to GNAS imprinting defect |

| Key features of clinical phenotype | Obesity, often severe | Early-onset obesity | Slightly low for birth weight | Sleep apnoea | Overweight/obesity can occur in adults but milder than in PHP1A | Early-onset obesity | Macrosomia at birth | Subcutaneous ossifications are very rare | Normal stature as adult | Severe short stature |
|---------------------------------|----------------------|-------------------|-----------------------------|--------------|-------------------|-------------------|-------------------|---------------------|-------------------|------------------|
| Short stature as adult | Short stature as adult | Subcutaneous ossifications | Subcutaneous ossifications | Subcutaneous ossifications | Normal stature as adult | Subcutaneous ossifications are the only sign | Normal stature | Subcutaneous ossifications can penetrate deeper into connective tissue, muscle, and other tissues | No subcutaneous ossifications | Severe short stature |
| Brachydactyly | Brachydactyly | Occasional mild brachydactyly | No brachydactyly | No brachydactyly | No associated deficits | No associated deficits | No associated deficits | No associated deficits | Severe short stature |
| Cognitive deficits common | Cognitive deficits unclear | Cognitive deficits unclear | Cognitive deficits unclear | Cognitive deficits unclear | Cognitive deficits unclear | Cognitive deficits unclear | Cognitive deficits unclear | Cognitive deficits unclear | Cognitive deficits unclear |

**Table 1. Pseudohypoparathyroidism and related disorders**

*PHP1C: Exhibit features of AHO (generally milder) and have resistance to PTH, TSH (indistinguishable from PHP1A). Due to mutations in GNAS that may impair receptor coupling activity to Gαs, but not its basal activity; PHP2: Similar to PHP1A but with normal urinary cAMP excretion

References for overlap syndrome of PHP1A/POH (12,13).

Very rarely an acrodysostosis-like syndrome can be due to a GNAS mutation. GHRH, growth hormone-releasing hormone; TSH, thyroid-stimulating hormone.
Endocrinology and metabolism

Table 2. Management

Management of PHP1A (and PPHP for AHO manifestations only)

Hypocalcaemia and hyperphosphatemia: PTH resistance
- Diagnosis must be made in setting of normal 25-OH Vitamin D and Mg levels; check these levels regularly and correct if deficiencies
- PTH resistance is often not present until early childhood and sometimes later
- Calcium and phosphorus abnormalities can occur much later than initial appearance of elevated PTH
- Treat elevated PTH with activated vitamin D (calcitriol) divided twice daily with/without calcium (Ca) supplements (supplements depend on serum Ca level as well as dietary Ca intake)
- Maintain serum PTH levels in the mid to upper normal range (or slightly above normal range)
- Calcitriol can be given as liquid if there is a need to titrate dose precisely; liquid also useful if capsules are difficult to swallow
- Typically, Ca supplements can be weaned from initial doses needed at diagnosis, but adequate amount of Ca must always be provided in the diet and/or with supplementation (calcium carbonate preferable)
- If serum phosphate levels remain elevated, intake of dietary phosphorus should be restricted (e.g. dairy, meat)
- PTH, Ca and phosphate levels should be checked every 3 months in early childhood; every 4–6 months in later childhood onward
- Persistent elevation of PTH could increase bone resorption, but if PTH is too low, hypercalcemia can occur
- Hypercalcemia is not a significant problem as in hypoparathyroidism. Ca can be reabsorbed at the level of the distal tubules (imprinting occurs in the proximal renal tubules and distal tubules are spared)
- Stones/nephrocalcinosis is rare, but monitoring of urine Ca/creatinine excretion should be annual (more often if there is hypercalcemia)
- Ectopic intracranial calcifications can occur secondary to elevated Ca-phos product, often in basal ganglia; very rarely cause issues

Hypothyroidism: TSH resistance
- Elevation of TSH is first sign of impending hypothyroidism, and free thyroxine levels can be normal or low
- Aim to treat so that TSH and free thyroxine are within the normal range
- All infants with ‘congenital hypothyroidism’ diagnosis should be screened carefully for potential PHP1A – examine carefully for ossifications and/or if weight increases excessively on therapeutic levothyroxine; check a PTH, although usually normal early in life
- Check thyroid function tests approximately every 3 months in growing children. Can extend to longer intervals as child gets older

Short stature: premature epiphyseal fusion/lack of pubertal growth spurt/GHRH resistance (GH deficiency)
- Final adult height is compromised by premature epiphyseal fusion and lack of pubertal growth spurt in PHP1A and PPHP patients
- Short stature should NOT be used as a necessary sign in the diagnosis of children with PHP1A and PPHP, often not short as children
- GH deficiency occurs secondary to GHRH resistance in approximately two-thirds of patients with PHP1A and can contribute to adult short stature
- All patients with PHP1A should be tested for possible GH deficiency as part of standard of care even if not short
- Perform GH testing early if possible (as early as 3 years of age); epiphsyses can fuse early
- If patient is obese and/or has snoring, ENT evaluations and sleep studies are indicated to assess whether tonsillectomy/adenoidectomy needed prior to GH treatment (risk of tonsil/adenoidal hypertrophy with GH therapy)
- Consensus is to treat GH-deficient PHP1A patients with GH if there are no significant risk factors
- Bone ages are deceptive – can be markedly advanced for the hand/wrist and do not reflect pubertal status
- Cannot predict final adult height using bone age. Three-site bone age can be helpful, specifically knee bone age
- Standard starting dose of GH is 0.3 mg/kg/week divided daily (with routine monitoring of glucose, free thyroxine, and IGF-1)
- Linear growth and IGF-1 level should be monitored every 3–4 months, with titration of GH based on IGF-1 level and growth velocity
- For children born SGA or who are very small, GH treatment can be considered (typically higher doses than for GH deficiency)
- Treatment for adult GH deficiency is indicated if patient severely deficient or partially deficient with symptoms (much lower doses)

Gonadal dysfunction: LH/FSH resistance
- Typically does not manifest with increased LH/FSH levels
- Pubertal onset is at the normal time for both sexes but Tanner stage typically halted at Tanner III-IV (partial hypogonadism)
- Girls often have amenorrhea/oligomenorrhea; may require treatment with oestrogen – need to be cautious regarding DVT risk
- Boys not as obviously affected although may also have halt in Tanner stage advancement; occasional cryptorchidism
- Fertility difficult to assess due to cognitive/social impairments that impact family planning (mouse studies indicate decreased fertility)

Calcitonin and other resistances (such as glucagon)
- Typically not clinically relevant to management

Obesity/Metabolic issues
- Suspect PHP1A with early-onset obesity (also suspect PHP1B); obesity tends to be less impressive in adulthood
- Dietary management and exercise are helpful, although decreased resting energy expenditure makes obesity difficult to control
- Exercise needs to be encouraged at a pace that will be maintained; start slowly
- Dysglycaemia/metabolic syndrome can be present – monitor fasting glucose, haemoglobin A1c intermittently
- Obstructive and central sleep apnoea – monitor for snoring; sleep studies/ENT evaluations when indicated (especially if GH will be started); component of apnoea thought secondary to PHP1A itself
- Reactive airways more common with obesity
| Table 2 (Continued) |
|---------------------|
| **Management of PHP1A (and PPHP for AHO manifestations only)** |
| **Brachydactyly** |
| - Common due to shortened metacarpals/metatarsals |
| - Causes fine motor issues, gross motor delays (also due to cognitive/developmental delays) |
| - Increased prevalence of carpal tunnel syndrome |
| - Physical therapy, occupational therapy and orthopaedics intervention are often necessary |
| **Subcutaneous ossifications (SCO)** |
| - Can occur spontaneously or with constant pressure/trauma from birth onward |
| - Avoid removal – can grow back and become even larger |
| - SCO excision can be considered if there is limitation of joint mobility, activities of daily living or causing severe pain |
| - No definitive treatment – NSAIDs and bisphosphonates have not proven successful long-term |
| - Worse in males than in females and tend to worsen with age |
| - Associated more with nonsense and frameshift mutations of GNAS |
| - Similar severity among family members |
| **Orthopaedics evaluation** |
| - Increased risk of lumbar stenosis and other orthopaedic issues |
| - Increased prevalence of carpal tunnel syndrome (see brachydactyly) |
| **Dental/Craniofacial abnormalities** |
| - Dental check-ups every 6 months |
| - Orthodontia commonly needed |
| - Mild midface hypoplasia can be present |
| - Round face out of proportion to weight |
| - Craniosynostosis/ Chiari I malformation can occur |
| **ENT abnormalities** |
| - Frequent otitis media |
| - Tonsillectomies/adenoidectomies common |
| **Genetic testing and counselling** |
| - Testing for genetic confirmation is possible through commercial diagnostic laboratories |
| - Important to address counselling issues early; evaluate family members for possible unrecognized PHP1A and PPHP |
| **Neurocognitive/psychosocial abnormalities** |
| - Wide spectrum of cognitive impairments and developmental delays from quite minimal to severe |
| - Behavioural abnormalities are common such as ADHD, anxiety, outbursts |
| - Early intervention with neurocognitive and psychosocial testing is important for appropriate interventions and school placements |
| - Educational support and developmental therapies important; occupational, physical and speech therapies |
| - Speech apraxias common |
| **Transition to adult care/support and advocacy** |
| - Need for continuity of care – ideally, specialist in field who carries patient throughout transition to adulthood (and beyond if possible) |
| - Concern about independent living – often live in group homes and/or with families |
| - Difficulty maintaining jobs |
| - Need medical team to advocate, help with disability and insurance claims. Support at home typically needed |

**MANAGEMENT OF PPHP (for non-AHO findings)**

**Possible progressive osseous heteroplasia (POH)**
- If diagnosed as a child, be aware that POH can evolve from what was thought to be PPHP (can be a spectrum)

**Small for gestational age (SGA)**
- Typically SGA as infants
- GH can be considered for SGA indication if patient meets approved criteria (typically higher dose than for GH deficiency)

**Genetic counselling**
- PPHP can have very subtle presentation – often diagnosed in mother who presents to clinic with her child with PHP1A
- Evaluate other family members for possible unrecognized PHP1A and PPHP

**MANAGEMENT OF PHP1B**

**Hypocalcaemia and hyperphosphatemia: PTH resistance**
- Treatment is same as in PHP1A for PTH resistance
- Seizures occur more frequently at presentation than in PHP1A because there are fewer physical stigmata to enable diagnosis early
As denoted by its name, AHO is an osteodystrophy. Classically, there is brachydactyly due to shortening of the metacarpals and metatarsals most often involving metacarpals/metatarsals III, IV and V, although any can be involved, as well as the distal phalanx of the thumb, which is often broad and short (Fig. 1a–d). These features are often a key to diagnosis, particularly for patients with PPHP who may have no other signs. The most frequent presentation for PPHP occurs when a mother brings her child with PHP1A to clinic and is then noticed to have physical features of AHO that were not previously considered medically significant. The proposed mechanism of the brachydactyly is ineffective PTHrP receptor signal transduction resulting in accelerated differentiation of chondrocytes [18–20]. The brachydactyly is usually not apparent in infancy but evolves over time and is variable even among family members. Another important manifestation of AHO is Archibald’s sign: when making a fist, there is absence of one or more knuckles (Fig. 1e). All of these hand/foot abnormalities can lead to problems with fine and gross motor activities [2] as well as carpal tunnel syndrome [21] and other orthopaedic issues [2,22].

Adult short stature occurs in both PHP1A and PPHP and is partly due to early closure of the epiphyses of the long bones secondary to premature chondrocyte differentiation. This typically begins near the start of adolescence (ages 9–13 years), at which time there is rapid advancement in the bone age and lack of a pubertal growth spurt [2,6,23–25]. However, during most of childhood, children are often NOT short. Therefore, short stature in childhood should not be used as one of the diagnostic criteria. Unfortunately, many children are diagnosed late due to this misconception (personal observation). All adults have shortened final heights if no interventions are taken. On occasion, the advanced bone age in children is misconstrued as early-onset puberty, and patients are inadvertently started on GnRH agonists (personal observation). Because of the shortened hand bones, the hand/wrist bone age is often advanced [26,27] (even as early as 2 years of age, personal observation) and is ahead of the knee bone age, which is usually more accurate, although adult height cannot be predicted [2,23,25]. The biallelic expression of GNAS in bone and chondrocytes likely explains the similar phenotype of short stature and brachydactyly in both PHP1A and PPHP [18,19,28]. Growth hormone (GH) deficiency due to GHRH resistance is frequent

### Table 2 (Continued)

| MANAGEMENT OF PHP1B |
|---------------------|
| **Hypothyroidism: TSH resistance** |
| - TSH resistance occurs in a subset of PHP1B patients and is mild (not as common as in PHP1A); treatment as above for PHP1A |
| **Calcitonin resistance** |
| - Typically not clinically relevant to management |
| **Growth** |
| - Macrosomia at birth, shortened or absent pubertal growth spurt, normal final height |
| - Typically no need for GH treatment – no GHRH resistance |
| **Obesity** |
| - Suspect PHP1B with early-onset obesity or macrosomia at birth |
| - Can be overweight/obese as adults, especially women (typically not the severe obesity as in PHP1A) |
| **Brachydactyly** |
| - Only in a subset, milder than in PHP1A |
| **Dental abnormalities** |
| - Dental check-ups every 6 months |
| **Genetic counselling** |
| - GNAS methylation and STX16 testing available |
| **Subcutaneous ossifications and Neurocognitive/psychosocial abnormalities** |
| - No significant issues in general |

FSH, follicle-stimulating hormone; GHRH, growth hormone-releasing hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone
Another striking feature of PHP1A and PPHP is the development of SCOs that can be painful and impair activities of daily living (Fig. 2) [2,29]. These ossifications are unique to disorders involving mutations in GNAS and are often a key to diagnosis. SCO can range greatly in size and number and can occur spontaneously as early as birth; they frequently occur in areas of trauma/pressure, such as the heel, belt area or bridge of the nose from glasses. When in isolation, the condition is termed osteoma cutis, but this can also be the first sign of a more severe PHP disorder (Table 1). In a recent investigation of 67 AHO patients monitored for development of these SCO over a 16-year time span [30], about 70% of AHO patients were found to have SCO, with the same frequency seen in PHP1A and PPHP. Males are more affected than females, and a greater severity of SCO is found in patients with frameshift and nonsense mutations. Severity within families is similar, and SCO tend to worsen with age. There is no definitive treatment, and removal can cause regrowth that is worse [30].

**FIGURE 1.** Brachydactyly can be varied and asymmetric in AHO. (a) Hands of patients with AHO showing the great variation that can occur in the affected phalanges/metacarpals. All of the hands are those of adults, showing the extreme variation in hand size as well. (b) Feet of patients with AHO (children and adults) showing the great variability in presentation. (c, d) Asymmetry within an individual’s hands and feet is commonly observed. (e) Classic fourth metacarpal shortening often associated with AHO (Archibald’s sign shown on right).
DIFFERENCES BETWEEN PSEUDOHYPOPARATHYROIDISM TYPE 1A AND PSEUDOPSEUDOHYPOPARATHYROIDISM

The differences in phenotype between PHP1A and PPHP reflect differences in the expression of the maternal versus paternal alleles in different tissues. This was shown through extensive investigation of murine models with heterozygous disruption of Gnas exon 1 or exon 2 (homozygous is lethal) as well as human studies showing evidence of tissue-specific silencing of Gαs expression from the paternal allele. The imprinting is partial in most tissues, with preferential expression of the maternal allele in the renal cortex, thyroid, gonad and pituitary, thereby causing the hormonal resistances to PTH, TSH, LH, FSH, and GHRH, respectively; there is biallelic expression in other tissues such as skin, renal medulla, heart, adipocytes, chondrocytes and bone [18,23,24,28,31–39]. As previously mentioned, dorsomedial hypothalamic imprinting has recently been shown to be the basis of the severe obesity that is present in PHP1A but not in PPHP [9,10*,40].

FIGURE 2. Subcutaneous ossifications in AHO. (a, b) Arrows on radiographs of the hand and leg point to multiple, small SCOs. (c) Surgically removed SCOs from a patient with AHO. (d) Subcutaneous ossified lesion showing the histology on haematoxylin & eosin staining consistent with bone and bone marrow elements from the fragments in (c). (e) Striking area of multiple subcutaneous ossifications near the knee and in the lower thigh on a radiograph of a patient with PHP1A. Many of the small lesions could be palpated easily. (f) Early SCOs can often present as blue-tinged lesions. (g) Cluster of SCOs of varying sizes seen on the hand of a patient with PHP1A. This composite has not been published before; however, some of the photos were used in other composites previously published; all photos taken by author, Emily Germain-Lee. Image (a) previously published as part of a different composite [2]. Images (c, d) previously published alone: [29]. Images (b, f, g) previously published as part of a different composite: [30*].
Hormonal resistance

Parathyroid hormone resistance

PTH resistance is the hallmark of PHP1A. It is typically not present at birth and develops later in childhood with an elevation in PTH usually followed by hyperphosphatemia and then hypocalcaemia, although some patients do not develop hypocalcaemia until later (for review, [2]). This emphasizes the need to screen for maternal GNAS mutations in the absence of PTH resistance with resulting normal or low thyroxine levels. The TSH resistance is mild due to partial imprinting in gonadal tissue and it is not consistently observed [45]. Although it is difficult to assess the true reproductive fitness of PHP1A patients due to their cognitive and social issues (see below), studies in Gnas exon 1 knockout mice have revealed significantly reduced fertility in females with maternally derived disrupted alleles (and minimally in those with paternally derived disrupted alleles) [31].

Thyroid-stimulating hormone resistance

TSH resistance is very commonly associated with PTH resistance with resulting normal or low thyroxine levels. The TSH resistance is mild due to partial imprinting in the thyroid [35–37] and presents without a goitre. It is often detected in infants during the newborn screen, being mistaken for congenital hypothyroidism. An infant with a ‘positive’ congenital hypothyroidism screen and ossifications should immediately trigger screening for PHP1A. In general, if an infant or child with hypothyroidism is being successfully treated with levothyroxine but continues to have an excessive increase in weight, the possible diagnosis of PHP1A should be entertained.

Luteinizing hormone/follicle-stimulating hormone resistance

Patients with PHP1A have evidence of hypogonadism and incomplete sexual maturation [45], most likely due to partial imprinting in gonadal tissue [36], but pubertal onset occurs at the usual time. Amenorrhea or oligomenorrhea is common in women [45,46], and oestrogen therapy is often needed, being aware of the potential risk of DVT formation (personal observation). Elevated LH/FSH levels would be expected in the face of gonadotropin resistance, but this is not consistently observed [45].

Growth hormone-releasing hormone resistance

A markedly increased prevalence of GH deficiency occurs in PHP1A (about two-thirds of patients) due to resistance to GHRH secondary to partial imprinting in the pituitary [2,23,24,38]. Treatment with recombinant GH results in an increased growth velocity [23,25,47,48] in PHP1A. A long-standing clinical trial of GH treatment in GH-deficient children with PHP1A through final height [49] is showing promising preliminary results with a significant increase in final adult height compared with untreated GH-deficient PHP1A adults [48, unpublished observation]. Testing for GH status, as well as recombinant GH treatment for GH-deficient PHP1A patients, is part of the 2018 Consensus guidelines [17**]. All PHP1A patients with moderate to severe obesity and/or snoring were screened with ENT examinations and sleep studies prior to treatment in the aforementioned GH trial, as GH treatment carries the potential risk of worsening obstructive sleep apnoea (OSA), such as from tonsillar/adenoidal hypertrophy [48,49]. This is important to include in standard of care treatment of GH-deficient PHP1A patients with recombinant GH (personal experience).

Although GH deficiency contributes to short stature in about two-thirds of patients with PHP1A, the premature fusion of the epiphyses has a large impact on the final adult height, as previously discussed. A study of GH-sufficient PHP1A children treated with GH is still underway in order to determine the effect on final adult height of increasing growth velocity maximally prior to the premature epiphyseal fusion [49]. Overall, it has been noticed that GH treatment does not increase ossification growth [30*] or have atypical side effects [48,49].
Other resistances
Calcitonin and glucagon resistances have also been reported [7,39] but are not as common as other hormonal resistances. ACTH resistance is typically not seen [7,24].

Obesity

Obesity and hypothalamic imprinting
Classically, the obesity in AHO had been described as occurring similarly in both PHP1A and PPHP. However, approximately a decade ago, severe obesity was found to be a feature of PHP1A only and not PPHP [8]. This was the first indication that hypothalamic imprinting may be involved. Early-onset obesity was also significant. Morbid obesity without evidence of hyperphagia was identified [2,50], and it was discovered that the cause of rapid weight gain in childhood was not hyperphagia but rather a decrease in resting energy expenditure (REE) [51,52,53*]. In adults with PHP1A, there are higher rates of type 2 diabetes and reduced insulin sensitivity compared with obese controls [54]. However, it was recently reported that children with PHP1A are at a high risk for dysglycaemia without reduced insulin sensitivity and have lower HgbA1c levels than controls. Interestingly, these children seem to have an increased sucrose preference as well [53*].

The obesity phenotype had also been demonstrated in Gnas exon 1 knockout mouse models [31,32]. Elegant studies of tissue-specific knockout models by Chen et al. [40] since that time have shown that the obesity is due to hypothalamic paternal imprinting of Goα in the central nervous system (CNS). They recently identified this as being specific to the MC4R-expressing cells of the dorsomedial hypothalamus and demonstrated that Goα is necessary for control of energy balance, thermogenesis and peripheral glucose metabolism with no impact on food intake, thereby correlating with the human phenotype [9,10**].

Obesity and sleep apnoea
The prevalence of sleep apnoea in PHP1A (including both OSA and central apnoea) was found to occur at a 4.4-fold greater relative risk than similarly obese children in a retrospective study, which was out of proportion to the obesity alone [55]. A recent prospective study revealed that significant OSA occurred in 60% of children with PHP1A and seemed amplified possibly due to their craniofacial issues, along with an increased prevalence of hypotonia and asthma [22,56*].

Cognitive, behavioral and developmental abnormalities in pseudohypoparathyroidism type 1A and pseudopseudohypoparathyroidism
In 1986, Farfel and Friedman [57] reported that reductions in Goα levels were associated with cognitive impairment, with 47–75% of patients with PHP1A having intellectual disability. Twenty years later, the estimate was nearly 79% of affected individuals [42,58]. The cognitive deficits range from minimal learning disabilities to severe impairment [2,42,59,60,61*,62] often requiring early interventions and therapies [61*,62]. In a study of PHP1A children, lower intelligence quotient (IQ) scores (full scale, nonverbal, verbal) and impaired behavioural, adaptive, attention and executive function scores were identified, along with stronger nonverbal abilities than verbal [49,62,unpublished observations]. In a recent study with comparisons to siblings and age-matched controls, 16 PHP1A children were found to have significantly lower IQ scores (25% composite IQ <70) for both verbal and nonverbal IQ. There were also executive and adaptive function deficits and ADHD [61*].

Patients with PPHP have overall higher social functioning as adults than those with PHP1A (unpublished). Interestingly, studies in mice demonstrated that females with a maternally inherited mutation neglected their young, resulting in nearly 80% mortality among pups before weaning, in contrast with those with a paternally inherited mutation, which showed normal mothering behaviour. This suggests the possibility of abnormal behaviour due to paternal imprinting in the CNS [31]. Cognitive testing in a single kindred with AHO implicated imprinting, with PHP1A family members being more affected than those with PPHP [58], although this study was limited by the small number of patients and by the use of a single measure for cognitive function. Abnormalities in olfaction and hearing have also been reported in PHP1A and are not present in PPHP [63–66], suggesting the involvement of GNAS imprinting in other parts of the CNS.

Overall, the cognitive and behavioural issues can lead to difficulties with independent living in adulthood, and a tremendous amount of support and advocacy from the medical team is needed for the patients and their families long-term (personal experience and [67*]).

**PSEUDOHYPOPARATHYROIDISM TYPE 1B**

PHP1B is characterized by PTH resistance without clear AHO signs or other hormonal resistances, although these patients have occasional mild
brachydactyly and mild TSH resistance [42]. Recently, early-onset obesity was defined as an important feature of PHP1B by Grüters-Kieslich et al. [68*], and in a small kindred of three PHP1B children, decreased REE and dysglycaemia were recently reported, similar to PHP1A [53*]. These findings further emphasize the overlap in the PHP disorders. Ossifications are very rare in PHP1B (none seen by author), and cognitive issues are not typically observed. Recently, bone mineral density studies of 48 patients with PHP1B stressed that PTH needs to be maintained at appropriate levels when treating to avoid adverse effects on bone [69*].

PHP1B is typically due to methylation defects at one or more of the GNAS promoter regions (see Table 1; [6,70,71]). Fifteen to 20% of PHP1B cases are autosomal dominant caused by a recurrent 3-kb deletion removing a genomic region upstream of GNAS that contains STX16. However, most cases are sporadic [71]. Methylation testing as well as targeted testing for the STX16 deletion are available for diagnostic confirmation of PHP1B.

**DIFFERENCES IN BIRTH WEIGHTS AND GROWTH PARAMETERS BETWEEN PSEUODOHYPOPARATHYROIDISM TYPE 1A, PSEUDOPSEUODOHYPOPARATHYROIDISM AND PSEUDOHYPOPARATHYROIDISM TYPE 1B**

A recently published investigation of a large group of PHP patients by Hanna et al. [72*] involved analysis of growth data from an international collaboration that reviewed 242 PHP1A, 64 PPHP and 220 PHP1B patients, all molecularly confirmed. This is an informative study, although one caveat is that the TSH, GHRH and medication status of these patients were unknown, which could impact these data. Patterns were found in PHP1A that revealed birth weights slightly below the mean with a striking increase in BMI by 1 year of age; this weight gain continued into childhood. There was absence of a pubertal growth spurt and poor final adult height in spite of an often normal height when younger, as described by others previously [2,3,23,25]. BMI z-scores were increased in adulthood, consistent with prior findings in smaller studies [2,8], with women much heavier than men. The PPHP infants were born small for gestational age (SGA) as previously reported [73]; they then had moderate catch-up growth but later had no pubertal growth spurt with ultimate short adult heights. PHP1B patients had macrosomia at birth and an increased BMI and growth velocity in childhood; they then had a shortened or absent pubertal growth spurt but normal final heights. They were overweight/obese as adults but not as severe as PHP1A. This study emphasizes the unique growth patterns within the PHP disorders and that the early-onset obesity of PHP1A and PHP1B can persist through adulthood, suggesting that dietary control should start very early in life and be maintained.

**CONCLUSION**

This review provides the background necessary to understand PHP1A, PPHP and PHP1B within the framework of recent advances and management of the conditions. A summary table is provided as a practical management tool for use in clinic. In addition, the spectrum of other PHP disorders is introduced. As we learn more about PHP, it is clear that there is an overlap between the various types. These disorders are complex and require comprehensive management. Being an advocate for these patients is vital to improving their quality of life. The 2018 international Consensus Statement is a major stride in improving patient care.

**Acknowledgements**

The author wishes to thank Alexzandra Buscarello, B.S. (Clinical Research Assistant II) for her help in preparation of the references, figures and formatting of this review. The author’s research that is mentioned within this review was supported by U.S. Food and Drug Administration Office of Orphan Products Development Grants R01 FD-R-002568 and R01 FD-R-003409 (both to E.L.G-L.) and National Institutes of Health Grant R21 HD078864 (to E.L.G-L.).

**Financial support and sponsorship**

None.

**Conflicts of interest**

There are no conflicts of interest.

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