Recommendations for Diagnosis and Treatment of Pseudohypoparathyroidism and Related Disorders: An Updated Practical Tool for Physicians and Patients

Recommendations on pseudohypoparathyroidism and related disorders: an updated practical tool for physicians and patients

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Abstract

Pseudohypoparathyroidism (PHP) and related disorders comprise metabolic diseases characterized by physical findings that variably include short bones, short stature, a stocky build, early-onset obesity and ectopic ossifications, as well as endocrine resistance primarily to parathyroid hormone (PTH). Beside these alterations, patients may experience over life other endocrine deficiencies due to hormone resistance leading to hypothyroidism, hypogonadism and GH deficiency, growth impairment independently of hormonal status, metabolic syndrome, skeletal issues with potential severe limitation of mobility and cognitive and psychomotor impairment.

PHP and related disorders are primarily clinical diagnoses. However, confirmation by molecular diagnosis is critical for patients and relatives, allowing the characterization of the subtype of the disease and guiding appropriate management including prevention of complications, screening and treatment of endocrine deficits and appropriate genetic counselling.

Starting from the recent publication of the first international consensus statement on these disorders, this article provides an updated and ready-to-use tool that may help physicians and patients to establish the main interventions as well as their timing.

Overall, a coordinated and multidisciplinary approach is highly recommended from infancy through adulthood, including a transition program.

Introduction

Much progress has been made since in 1942 when Albright and colleagues described pseudohypoparathyroidism (PHP) as a novel disorder of hormone resistance in which hypocalcemia and hyperphosphatemia were due to decreased responsiveness to parathyroid hormone (PTH). In addition, patients also manifested an unusual appearance characterized by short stature, brachydactyly, obesity with a round face, and heterotopic ossification, which came to be known as Albright hereditary osteodystrophy (AHO)[1]. Advances in the early years focused on clinical aspects, leading to the identification of the constellation of disorders associated with a spectrum of abnormal physical characteristics as well as neurocognitive and endocrine abnormalities including the different subtypes of PHP (i.e., PHP1A, PHP1B, PPHP, POH). Today the term pseudohypoparathyroidism (OMIM #103580 for PHP type 1A (PHP1A), #603233 for PHP type 1B (PHP1B) and #612462 for PHP type 1C (PHP1C)) describes disorders that share in common the presence of functional hypoparathyroidism, with hypocalcaemia and hyperphosphataemia, that is the result of resistance of target tissues to PTH. In some cases, resistance to other hormones (such as thyroid-stimulating hormone (TSH), gonadotropins, growth-hormone-releasing hormone and calcitonin) also occurs. Patients with PHP1A and PHP1C can also manifest features of AHO, in which defects in chondrocyte and osteoblast differentiation lead to early closure of growth plates, accounting for brachydactyly and short stature, and development of heterotopic bone. Years after the description of PHP Albright described patients in whom only the physical features of AHO were present and who had normal PTH responsiveness. Albright originally termed this condition pseudopseudohypoparathyroidism (PPHP), but today , we classify these patients as having pseudopseudohypoparathyroidism (PPHP; OMIM #612463), progressive osseous heteroplasia (POH; OMIM #166350) or osteoma cutis depending upon the extent of the heterotopic ossification and brachydactyly [2]. More recent studies have further refined the phenotype of these related disorders and have described other associated features such as intrauterine growth failure[3], early-onset obesity[4], cognitive impairment mainly affecting verbal skills[5].

The development of sophisticated biochemical and molecular techniques led to the recognition that other developmental disorders that share features of PHP, , such as

acrodysostosis (OMIM #101800) [6,7] are due different defects in a shared pathway in which hormones bind to heptahelical transmembrane receptors that are coupled via the stimulatory G protein (Gs)[8] to activation of adenylyl cyclase with consequent increases in cyclic AMP (cAMP)-dependent signaling. , We can now identify *de novo* or inherited genetic or epigenetic mutations within various genes (e.g. *GNAS*[2,9,10], *PRKAR1A*[7], *PDE4D*[6,11] or *PDE3A*[12]) encoding proteins in this pathway in around 80-90% of patients with PHP or related disorders[13,14] (Figure 1).

Since publication of the original Consensus Statement for PHP and related disorders[15], some new relevant finding have been published. Therefore, with the aim of disseminating and updating the international consensus statement, the three main investigators (AL, GM and GPdN) invited the 37 previous experts to collaborate in this shortened and updated paper. All (or X) of them actively accepted.

Literature search was updated from December 18th, 2016 to 31st August, 2019 using the same key terms as in the previous version, leading to a total of more than 1000 articles.

The addition of the recently published evidence did not modify the content of the previously published recommendations but further strengthened the background underlying them and prompted us to provide a summarized and practical tool to physicians and patients.

Clinical diagnosis and management

PHP and related disorders have defects in the cAMP signaling pathway downstream of the heptahelical receptors for PTH/PTHrP and other hormones and neurotransmitters. Despite this common molecular umbrella, presentation and disease severity vary considerably between affected individuals, even among patients carrying the same genetic alteration, highlighting the important clinical and molecular overlap of these diseases. Newborns and young infants usually present with unspecific features such as being born small for gestational age (SGA)[16], early onset obesity[3] or transient hypothyroidism. In the absence of familial history or typical symptoms such as ectopic ossifications, diagnosis may be delayed for years due to lack of recognition of the syndrome and associated features. Later in life, growth failure, brachydactyly, obesity,

hypocalcemia and/or seizures often lead to investigations and identification of the underlying cause.

Therefore, diagnosis of PHP and related disorders should be based on clinical and biochemical characteristics, and, in some cases, on the family history. The main clinical criteria for AHO include brachydactyly type E due to premature fusion of the epiphyses and short stature by adulthood; patients may have additional features such as ectopic ossifications, a stocky build and/or round face.

In order to diagnose a patient with PHP or related disorder, the following major features should be present: PTH resistance, and/or ectopic ossifications, and/or early-onset (before 2 years of age) obesity associated with TSH resistance, and/or AHO. In addition, other features can be considered as supporting the diagnosis of PHP and related disorders: unexplained primary hypothyroidism without a goiter, hypercalcitoninaemia, hypogonadism, growth hormone deficiency, cognitive impairment, hearing impairment, craniosynostosis and neurosurgical features, tooth ankylosis, oligodontia, cataract and/or CNS calcifications, sleep apnoea, ear infections, asthma, and restricted fetal growth (Figure 2).

PHP and related disorders are primarily clinical diagnoses. However, molecular analyses are critically important for genetic counselling and in some cases for diagnosis particularly when there is significant overlap in clinical features (e.g. PHP1A versus acrodysostosis). . Nowadays, the genetic or epigenetic diagnosis relies on the most likely identified causes of the disease at the time of analysis according to the algorithm (Figure 3). The use of genetic ad epigenetic analyses to diagnose patients with PHP and related disorders has reduced the need for administration of exogenous PTH or assessment of Gsα bioactivity. Altogether, this will guide appropriate management including prevention of complications, lifestyle adjustments, screening and treatment of endocrine deficits and appropriate genetic counselling.

It is worth mentioning that we lack sufficient prospective clinical trials and outcomes data in patients with PHP and related disorders to provide evidence-based guidelines for management. Because of their rarity, it is difficult to recruit the large numbers of patients are needed to evaluate the natural history or treatment outomes of the diseases. A multi-disciplinary follow-up and early, specific interventions are necessary for efficient therapeutic management of these patients. We have summarized in this

document (see below) and in table 1, the main interventions that should take place during the follow-up of patients with PHP and related disorders.

Resistance to PTH

PTH resistance is the sina qua non of PHP, found in 45-80%[17], particularly in those with PHP1A. It is defined as the association of hypocalcaemia, hyperphosphataemia and elevated serum levels of PTH in the absence of vitamin D deficiency, abnormal magnesium levels and renal insufficiency[15].

Variable degrees of PTH resistance with either normo- or hypocalcemia are present in patients with PHP1B [18–21], as well as in acrodysostosis patients with mutations in *PRKAR1A*[6,7,11,15,22,23], being usually absent in those with *PDE4D* mutations [6,11,15,22,24,25].

PTH resistance in the context of PHP and related disorders should be suspected when PTH is at, or above, the upper limit of normal, in the presence of normal plasma concentratons of magnesium and calcifediol even in the absence of hypocalcaemia and hyperphosphatemia. In fact, at least in patients with PHP1A, resistance to PTH is usually absent at birth, and evolves over life (from 0.2 to 22 years)[9,26,27]. Usually, PTH levels starts to rise, then plasma levels of phosphorus (and occasionally calcitriol) increase, followed by hypocalcemia within an interval of up to 4.5 years after the first biochemical abnormality[28]. Renal excretion of phosphorus is low, but renal reabsorption of calcium is high, reflecting the resistance to PTH in the proximal but not distal renal tubule cells. Therefore, when PTH levels are elevated, urine levels of calcium are low whereas calcitriol levels might be either low or normal[9].

Typically, the skeletal manifestations in PHP occur later, being intensified during periods of rapid growth with associated increased calcium requirement[26] .

For these reasons, at diagnosis and before initiation of treatment, monitoring of mineral metabolism is recommended. Measurement of PTH, calcium and phosphorus should be performed regularly, every 6 months in children and at least yearly in adults. Monitoring should be more frequent in symptomatic individuals, during acute phases of growth, acute illness and during pregnancy and breastfeeding, when dose requirements for active vitamin D metabolites or analogues might change. Normal levels of 25-OH-vitamin D should be achieved in all patients[15].

When PTH levels reach more than twice the upper level of normal, treatment with active vitamin D analogues should be considered, independently of the presence of

hypocalcaemia. Calcium supplements should be prescribed, depending on the calcium dietary intake.

Management of severe symptomatic hypocalcaemia does not differ from that of hypoparathyroidism[29]. Activated forms of vitamin D such as calcitriol or the alfacalcidol plus (in most cases) oral calcium supplementation are the mainstay of treatment.

Treatment of hypocalcemia associated with PTH resistance differs from that of primary hypoparathyroidism[29] as one can target a higher serum level of calcium; as long as serum levels of PTH are not suppressed there is little danger of hypercalciuria. In addition to the maintenance of levels of calcium and phosphorus within the normal range, while avoiding hypercalciuria, management should target PTH levels to mid-normal to up to two-times the upper limit of normal; higher levels of PTH might have adverse effects on skeletal mineralization or on the growth plate[30–33]. During treatment, levels of PTH, calcium and phosphorus should be monitored every 6 months in asymptomatic patients and more frequently when clinically indicated. Patients and/or their family should be instructed about signs of hypocalcemia and hypercalcaemia[15].

Patients with PHP and related disorders rarely develop hypercalciuria and/or nephrocalcinosis because of the preserved responsiveness of the distal renal convoluted tubules to PTH [26,34,35]. However, episodes of nephrolithiasis have been seldom observed (unpublished work) in patients with PHP1A and PHP1B, particularly after completion of pubertal growth. Monitoring of urine calcium levels is recommended at regular intervals during treatment, as well as appropriate renal imaging in patients with persistent hypercalciuria on repeated measurements[15,29].

Chronic hypocalcaemia with hyperphosphataemia can result in an elevated calcium x phosphorus product, which can lead to ectopic calcification (not to be confused with the ectopic *ossification* of AHO that occurs without relationship to serum levels of calicium an phosphorus). Intracranial calcifications of the basal ganglion can resemble those that occur in Fahr syndrome due to mutations in the *SLC20A2* gene, but patients with PHP will also have calcification of the cerebral white matter [17]. So far, brain calcifications have not been described in patients with PPHP, POH or those with a mutation in the *PRKAR1A* or *PDE4D* genes[6,7,36–39]. Ectopic depositions of calcium and phosphorus may also occur in the eyes leading to posterior subcapsular cataract or corneal opacities[39–43]. Brain CT scan is indicated only when neurological manifestations

are present, while regular ophthalmologic examination is recommended to diagnose or manage cataracts.

Finally, PTH resistance is often associated with dental and oral features such as failure of tooth eruption, hypodontia, , malocclusion, gingival hyperplasia, gingivitis with spontaneous bleeding and pain[44,45]. Regular dental reviews, every 6-12 months at least during childhood, is recommended[15,46].

Ectopic ossification

Ectopic ossifications are found in 100% and 80–100% of patients with POH and PPHP/AHO respectively, 30–70% of PHP1A patients and very uncommonly in those with PHP1B, while they have never been reported in patients with acrodysostosis[24,47]. They should be therefore considered as a specific consequence of *GNAS* molecular alterations, particularly the paternally inherited ones[48] leading to Gsα deficiency in mesenchymal stem cells hence *de novo* formation of extra-skeletal islands of ectopic bone in the dermis and the subcutaneous fat[49,50].

No formal evidence exists to suggest that the inflammation or traumatic events lead to ectopic bone formation in *GNAS*-based conditions unlike fibrodysplasia ossificans progressiva (FOP)[51,52]. Nevertheless, it often occurs in locations subjected to high pressure loads, such as the heel[53].

POH is defined by ossifications located in and extending towards connective tissues, muscles, tendons and ligaments[48,52,54]. Differently, in *osteoma cutis*, PHP1A, PPHP or AHO, ectopic bone remains superficial.

Ectopic ossifications are uncommon in the general population, and the presence of these lesions should trigger a clinical and biochemical work up to search for signs of AHO, PTH and TSH resistance, or FOP. Skin biopsy is not necessary in obvious cases or contraindicated in case of suspicion of FOP.

As a result of the rareness of these conditions, limited information is available about prognosis and no effective treatments exist for the management or prevention of ectopic ossifications.

Cutaneous bony plaques should be investigated by careful examination at each visit, especially in patients with mutations on the *GNAS* paternal allele (POH and PPHP). Patients and families should be instructed about self-examination. Location and size of

ossifications, involvement of joints and impairment of movement and bone growth, predilection of lesions towards areas exposed to increased pressure due to weight bearing (feet and ankles), assessment of potential triggering events (trauma, infection, inflammation and surgery), and evolution during puberty or treatment with rhGH should be documented at each visit.

Imaging of ossifications should be performed using CT or MRI only when the lesions are painful, symptomatic, jeopardize joint or organ function or are being considered for surgical excision.

Physical therapy and meticulous skin care are critical for the prevention of development and/or progression of ectopic ossifications. Surgical excision should be considered in the presence of delimited, superficial lesions associated with pain and/or movement impairment, because of recurrence risk[15,52,54]. In ossifications involving joints, immobilization, e.g. through casts, should be avoided to prevent to ankyloses. No evidence support the use of non-steroidal anti-inflammatory drugs, bisphosphonates or steroids in primary or peri-surgical treatment of asymptomatic ectopic ossifications[15].

Brachydactyly

Brachydactyly is not specific to PHP and related disorders. Patients with PHP and related disorders, display the brachydactyly type E[55], however with a huge variability in frequency and severity. Brachydactyly is usually found in most, if not all, i.e. 70-80% of PHP1A, few, i.e. 15-33% of PHP1B, and all patients with acrodysostosis[15] (Figure 2).

It develops over time and might not be evident in early life, except in patients with acrodysostosis[7,56]. The clinical and radiological examination of the hands and feet from early childhood onwards is important to establish the diagnosis of brachydactyly, which can impair fine motor skills, such as handwriting[57]. In some patients occupational therapy and/or appropriate orthopedic devices may be indicated, e.g. special shoes and orthopedic insoles[15].

Additional bone features may be present such as carpal tunnel syndrome[57], Madelung deformity[58], spinal stenosis[59], acro-osteolysis, phalangeal cone-shaped epiphyses, and

craniosynostosis[60]. Depending on the functional consequences, they may require a specific multidisciplinary evaluation and orthopedic corrective surgery[15].

Management of growth and GH deficiency

The majority of PHP1A and PPHP patients display adult short stature, approximately -2.5 SD, despite having normal length/height during childhood[3]. Final height in acrodysostosis seems even shorter, on average -3.5 SD (-8.8 to -0.5)[15]. Noticeably, most patients with a paternal *GNAS* mutation (that is, patients with PPHP or POH) and patients with acrodysostosis show a restricted fetal growth, hence are born small for gestational age (SGA)[15]. Intrauterine growth restriction, advanced bone age, lack of pubertal growth spurt, and, in PHP1A, growth hormone-releasing hormone (GHRH) resistance and consequently GH deficiency, likely contribute to the premature cessation of growth and adult short stature[3,15]. Careful and regular monitoring of height, skeletal maturation and GH secretion starting around the age of 3-6 years is therefore advised in all affected children. Patients born SGA age who do not exhibit appropriate catch-up growth or patients with GH deficiency should be considered for treatment with rhGH[15]. Careful attention should be paid to the evolutions of ossifications in rhGH treated patients, although rhGH has not been identified as a risk factor for ossifications[47,52]. Data are needed to establish efficacy and safety of pubertal blockers to increase final height in these patients[61]. Differently, and despite an enhanced growth velocity during infancy, PHP1B patients display adult heights similar to that of the general population[3,62].

Obesity

Patients with PHP1A or PHP1B develop early-onset obesity, usually in the first 2 years of life; this may be the first and only symptom in many patients until diagnosis is made during adolescence or adulthood[3,4,63,64]. Several mechanisms are likely involved in the excessive acquisition and maintenance of fat mass including a defect in the Gsα-dependant melanocortin signaling pathway (maybe responsible for the patients hyperphagic trait[64]), a decreased resting energy expenditure compared with obese controls[65,64,66], a low sympathetic nervous system activity, decreased lipolysis[67], and growth hormone-releasing hormone resistance in the pituitary[68]. Overall, we know now that obesity or overweight are associated with all types of PHP and related disorders[15] with the exception of POH. Once diagnosis is made, BMI and eating behavior should be regularly monitored; patients, parents and families should be supported with psychological support and educational programs, as early as possible, even in

the presence of a normal BMI as a preventive strategy and taking into account the low resting energy expenditure of these patients[3].

Sleep apnoea is a well-known complication of obesity that was reported as more frequent in patients affected with PHP1A[69], and present in acrodysostosis[38]. In addition to obesity, these patients display round faces, and sometimes flat nasal bridge and/or maxillary hypoplasia[22,46] which could also favor the development of sleep and respiratory disturbances[65,69]. Therefore, all patients with PHP and related disorders should be evaluated for restless sleep, snoring, inattentiveness and daytime somnolence and, if present, polysomnography is recommended.

Metabolic syndrome

Decreased insulin sensitivity and hypertension are present in a large subset of adult PHP1A patients and may not be entirely related to obesity[70]. Lipid profile is not profoundly modified in PHP1A patients, but reports are limited[71]. Hypertension is frequently observed in young adults with PHP and related disorders[72] yet the incidence of cardiovascular diseases is not increased in cohort studies conducted in Denmark[39,71]. Overall, we propose to include measurement of blood pressure, lipid profile and glucose metabolism within the regular multidisciplinary follow-up of patients affected with PHP and related disorders.

Cognitive features

Cognitive impairment has been reported in 40-70% of patients with PHP1A, 0-10% of patients with PPHP or POH, as exceptional in patients with PHP1B and of variable prevalence in patients with acrodysostosis[15]. Performance studies have been done only in PHP1A and showed reduced scores in comparison to peers[5,73–75], predominance of the defect in language over gross motor skills and tendency to improve during late childhood[5]. In addition to the role of Gsα in brain development[76], neurological or neuropsychiatric manifestations may be attributed in some patients to organic CNS alterations, including Chiari 1 malformation[77–79] or prolonged periods of hypocalcemia[74,79]. Patients with PHP and related disorders should be referred to a neuropsychologist for neurocognitive and/or behavioral assessment at diagnosis or at pre-school age, especially in patients with PHP1A and acrodysostosis due to *PDE4D* mutations.

TSH resistance

Patients with PHP1A frequently (if not always[80]) have elevated serum levels of TSH and usually normal or only mildly depressed serum levels of thyroid hormone. Elevated levels of TSH due to TSH resistance is often present at birth, and detected on neonatal screening[15]. Most PHP1B patients display TSH levels are at the high end of normal or mildly elevated[15]. TSH resistance is present in patients with acrodysostosis due to *PRKAR1A* mutations but not in those with *PDE4D* mutations[22,24]. Despite a prompt diagnosis of hypothyroidism after birth and initiation of treatment does not seem to prevent the development of motor or cognitive delay[73].

Evaluation of thyroid function, including autoantibodies in adolescents and adults if hypothyroidism is present with a goiter, and early intervention is advised in all patients; treatment objectives do not differ from other causes of hypothyroidism[81]. TSH monitoring is recommended every 6 months in patients <5 years of age and yearly in older children and adults[15].

Alterations in gonadal function

Gonadal function and puberty

Resistance to gonadotrophins appears much more subtle than resistance to other hormones such as PTH and TSH suggesting that PHP1A patients display only partial resistance to gonadotropins[15,82]. Clinically, patients may present with menstrual irregularities in girls[82], cryptorchidism in boys([83] and experts' experience), and blunted or absent pubertal growth spurt in adolescents[3] with PHP1A. PHP1B and PPHP seem to have normal gonadal function[84], while variable resistance to gonadotropins has been described in patients with acrodysostosis and mutations in the *PRKAR1A* gene[22].

Tanner staging of sexual maturation and radiological assessment of bone age should be regularly performed in all patients with PHP or related disorders, as skeletal maturation is typically advanced in these children. Conversely, biochemical assessment of gonadal status is not recommended unless clinically indicated. Cryptorchidism and/or hypogonadism, when present, should be corrected and managed according to the standard recommendations[15].

Fertility and pregnancy

Unassisted and uneventful pregnancies have been reported in female patients with PHP1A[82] and PHP1B[85]; fertility is typically normal in women with PPHP or POH, who may give birth to offspring with PHP1A[15]. Infertility or the need for use of an assisted reproductive technique to obtain pregnancy have been reported[15]. Men with PHP1A have also fathered children (ref Levine and possibly others). Prenatal genetic diagnosis can be used to reduce the risk of having an affected child (Levine ref).

Pregnant women with PHP and related disorders should be monitored as any other pregnancy following the international guidelines in case of hypocalcemia and/or hypothyroidism. Vaginal delivery might not be possible if there is reduced pelvic size and decreased range of motion of the hips due to local ossifications[15]. The newborn should be evaluated for levels of TSH, calcium and phosphorus. Breastfeeding is not contraindicated, but close follow-up and clinical monitoring of the baby is advised[15].

Menopause and osteoporosis

There is no evidence that patients with PHP develop age-related osteoporosis. Nevertheless, these patients do have several potential risk factors for osteoporosis, e.g. hypogonadism, chronic elevation of PTH and GH deficiency. In particular, the exact consequences of the PTH signaling defect on bone in those patients is unclear, as several studies have shown that bone mass is increased in patients with PHP1a (ref) and PHP1b. Therefore, due to the lack of evidence of reduced bone density and/or increased fracture risk[86], there is no indication to perform routine DXA measurements in patients with PHP and related disorders[15]. If osteoporosis is diagnosed, management should be based on identification of an underlying cause for bone loss.

Other hormone resistances

Elevated calcitonin levels likely due to calcitonin resistance have been reported in PHP1A[87,88], PHP1B and acrodysostosis patients with *PRKAR1A* mutations[7]. They might be used to support the diagnosis of PHP and related disorder. Resistance to additional hormones that mediate their actions through Gsα-coupled receptors have also been previously reported; however, the clinical relevance of these abnormalities remains to be established[89]. Except for diagnosis purposes, screening of additional hormone

resistances, and calcitonin measurement, is not recommended in patients with PHP and related disorders[15].

Molecular diagnosis

The main subtypes of PHP and related disorders are caused by de novo or autosomal dominantly inherited inactivating genetic pathogenic variants within the genes of the PTH/PTHrP signalling pathway[8] or by epigenetic alterations at *GNAS* locus. *GNAS* presents four distinct differential methylated regions (DMRs): the paternally methylated *GNAS-NESP*:TSS-DMR and three maternally methylated *GNAS-AS1:*TSS-DMR, *GNAS-XL:*Ex1-DMR and *GNAS A/B:*TSS-DMR.

PHP1A is caused by inactivating pathogenic variants on the maternal allele of the *GNAS* gene, including both point variants and gene rearrangements[15,90,91], whereas when affecting the paternal allele mainly causes PPHP, but also *osteoma cutis* or POH[15,54]. Point variants can be easily detected by sequencing whereas genomic rearrangements can be analyzed by quantitative methods[92]. Determination of the affected allele in de novo cases is becoming relevant since few PPHP patients may also develop hormone resistance[93]. Regarding genetic counselling, patients with *GNAS* genetic variants have a 50% chance of transmitting the molecular defect and depending on their sex, the descendant will develop PPHP or POH (when the patient is male) or PHP1A (when the patient is female).

Decreased methylation at *GNAS A/B*:TSS-DMR is detected in all patients with PHP1B[15,94]. When it is the only affected DMR (15–20% of PHP1B cases)[14], it is mainly the consequence of an alteration in the maternal allele of *cis*-acting control elements within *STX16*[95]. Other maternally inherited deletions and duplications have also been identified in some rare familial cases affecting either an isolated *GNAS A/B:*TSS-DMR or all four DMRs[15]. This clinical form is classified as AD-PHP1B, due to its autosomal dominant mode of inheritance when maternally inherited (i.e., paternally inherited deletions are not associated with methylation defects)[95].

On the other side, sporadic PHP1B is often associated with methylation defects at additional DMRs, in addition to *GNAS A/B*:TSS-DMR, with no identified underlying genetic mechanism[96]. In around 8-10%[14,97] of these sporadic cases, the methylation defects are caused by paternal uniparental disomy of the chromosomal region comprising *GNAS* (UPD(20q)pat)[15,98]. In these patients, recurrence and transmission risks are expected to be similar to that of the general population.

Even if *GNAS* methylation defects can be detected through the use of several methods, a methylation sensitive-MLPA (MS-MLPA) kit from MRC-Holland (MS-MLPA ME031 GNAS) enables the detection at the same time of methylation defects at the different GNAS-DMRs as well as *STX16* and *NESP/AS* deletions and deletions encompassing *GNAS*[99].

Paternal uniparental isoDisomy can be identified either by microsatellite (STR) typing or SNP array.

So, in brief, in individuals with a suspected diagnosis of PHP, molecular diagnosis must include DNA sequence, methylation and CNVs analyses at the *GNAS* locus following the proposed algorithm described in Figure 3.

Acrodysostosis can be caused by heterozygous point pathogenic variants in *PRKAR1A* or *PDE4D*[6,7,11], so they can be easily detected by sequencing. They mostly occur *de novo*[15], so the recurrence risk is similar to that of the general population. As it presents an autosomal dominant way of inheritance, patients have a 50% of chance of passing on the molecular defect and the disease to their descendants.

Conclusions

Patients with PHP and related disorders may display over life a highly heterogeneous and progressing clinical picture which renders a multidisciplinary approach mandatory. Each of the many clinical aspects and potential complications of the disease should be managed by experts, when possible at referral centers. In addition, the different and complex genetic and epigenetic defects underlying these disorders also require a specialized approach in order establish a correct molecular diagnosis, which is now

often difficult and time-consuming for both patients and their families, but that might in turn help clinicians to look for specific clinical manifestations with consequent appropriate management.

Starting from the recent publication of the first international consensus statement on these disorders, this article provides an updated and ready-to-use tool for physicians and patients with Table 1 summarizing the main interventions as well as their timing.

Given the lack of strong evidence-based data, particularly for management of these patients, there is an urgent need to implement registries with large cohorts of patients, to better understand the natural history and the overlaps as well as the specificities of these clinically heterogeneous but closely related diseases and, finally, develop new therapies.

Legends of figures

Figure 1: Molecular defects in the PTH–PTHrP signalling pathway in PHP and related disorders. The main clinical features of PHP and related disorders are due to molecular defects within the PTH–PTHrP signalling pathway, with the exception, perhaps, of ectopic ossification. The diseases caused by alterations at the genes codifying the indicated proteins are shown in bold. Differential diagnoses are indicated in grey. PTHR1: PTH/PTHrP receptor type 1; G protein: trimer α, β, γ; cAMP: grey diamond; PKA: tetramer R (regulatory subunit 1A; dense grey) and C (catalytic subunit; light grey); phosphodiesterases: ovals PDE4D and PDE3A; PHP: pseudohypoparathyroidism; HTNB: autosomal dominant hypertension and brachydactyly type E syndrome; TF: transcription factor.

Figure 2: Main clinical features of PHP and related disorders. PHP and related disorders affect many organs unequally. The clinical and biochemical features of the main diseases have been represented with their frequency when known. PHP1A: pseudohypoparathyroidism type 1A due to maternal loss of function mutation at the *GNAS* coding sequence, PHP1B: pseudohypoparathyroidism type 1B due to methylation defect at *GNAS*; PPHP: pseudopseudohypoparathyroidism due to paternal loss of function mutation at the *GNAS* coding sequence; POH: progressive osseous heteroplasia due to paternal loss of function mutation at the *GNAS* coding sequence; ACRDYS1: acrodysostosis due to mutation in *PRKAR1A*; ACRDYS2: acrodysostosis due to mutation in *PDE4D*; SGA: small for gestational age.

Figure 3: Molecular algorithm for the confirmation of the diagnosis of PHP and related disorders. If patients present with an Albright hereditary osteodystrophy (AHO), genetic alterations at *GNAS* should be studied, including point mutations (sequencing) and genomic rearrangements (such as MLPA and aCGH). In the absence of AHO, epigenetic alterations should be analyzed first. According to the results obtained for the methylation status, further tests are needed to reach the final diagnosis: if the methylation defect is restricted to *GNAS A/B*:TSS DMR, STX16 deletions should be screened for, and, if present, the diagnosis of AD-PHP1B is

confirmed; if the methylation is modified at the four DMRs, paternal uniparental disomy of chromosome 20 [UPD(20q)pat] should be screened for; in absence of UPD(20q)pat, deletions at NESP should be screened for; if no genetic cause is identified as the cause of the methylation defect, the sporadic form of the disease (spor-PHP1B) is suspected. After exclusion of the *GNAS* locus as the cause of the phenotype, and in patients with AHO, PHP-related genes (that is, at least *PDE4D* and *PRKAR1A*) should be sequenced. RT-PCR: Reverse-Transcription Polymerase Chain Reaction; SNP: Single Nucleotide Polymorphism; NGS: Next-Generation Sequencing; A/B: *GNAS A/B:* TSS-DMR; STRs: Short Tandem Repeats (microsatellites); UPD: uniparental disomy; WES: Whole Exome Sequencing; WGS: Whole Genome Sequencing; ICR: imprinting control region; VUS: variant of unknown significance.

Table 1. Summary of the main interventions during the follow-up of patients with PHP and related disorders (adapted from Mantovani et al)[15]

Action points	Infancy Newborn - 2 years	Early childhood 2 - 6 years	Late childhood to adolescence	Adulthood
Anticipatory Guidance				
Family support	✓	✓	✓	**N/A**
Genetic counselling	at diagnosis	at diagnosis	at diagnosis	at diagnosis
Medical Evaluation				
Physical examination				
Linear growth	✓	✓	✓	**N/A**
Weight gain/BMI	✓	✓	✓	✓
Ectopic ossifications	✓	✓	✓	**S**
Development and/or cognition	✓	✓	**S**	**S**
Descended testis	✓	✓	If not checked before	If not checked before
Puberty	**N/A**	**N/A**	✓(biochemistry in case of retardation)	**N/A**
Psychosocial evaluation	**N/A**	✓	**S**	**S**
Blood pressure	**N/A**	✓*	✓	✓
Biochemical analyses				
Calcium-phosphorus metabolism	✓	✓	✓	✓
Thyroid	✓	✓	✓	✓
GH secretion	**N/A**	✓	✓	**S**
Glucose and lipid metabolism	**N/A**	✓	✓	✓
Fertility	**N/A**	**N/A**	**S**	**S**
Radiological studies				

Bone age radiography	**N/A**	✓ (in case of growth deceleration)	✓ (in case of growth deceleration)	**N/A**
Orthodontic and/or dental	**N/A**	✓	✓	**S**
Age-appropriate renal imaging	✓**	✓**	✓	✓**

✓ to be performed at diagnosis and annually thereafter; **S** Subjective (by history and physical examination); **N/A** Not applicable * At least 1 time year, with an appropriate sized cuff. ** Annually in case of increased excretion of urinary calcium or nephrocalcinosis

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Author contributions

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