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

Giovanna Mantovani[a], **Murat Bastepe**[b], **David Monk**[c], **Luisa de Sanctis**[d], **Susanne Thiele**[e], **S. Faisal Ahmed**[f], **Roberto Bufo**[g], **Timothée Choplin**[h], **Gianpaolo De Filippo**[i], **Guillemette Devernois**[h], **Thomas Eggermann**[j], **Francesca M. Elli**[a], **Aurora Garcia Ramirez**[k], **Emily L. Germain-Lee**[l,m], **Lionel Groussin**[n,o], **Neveen A.T. Hamdy**[p], **Patrick Hanna**[q], **Olaf Hiort**[e], **Harald Jüppner**[b], **Peter Kamenický**[q,r,s], **Nina Knight**[t], **Elvire Le Norcy**[o,u], **Beatriz Lecumberri**[v,w,x], **Michael A. Levine**[y,z], **Outi Mäkitie**[A], **Regina Martin**[B], **Gabriel Ángel Martos-Moreno**[C,D,E], **Manasori Minagawa**[F], **Philip Murray**[G], **Arrate Pereda**[H], **Robert Pignolo**[I], **Lars Rejnmark**[J], **Rebeca Rodado**[k], **Anya Rothenbuhler**[r,K], **Vrinda Saraff**[L], **Ashley H. Shoemaker**[M], **Eileen M. Shore**[N], **Caroline Silve**[O], **Serap Turan**[P], **Philip Woods**[t], **M. Carola Zillikens**[Q], **Guiomar Perez de Nanclares**[H], **Agnès Linglart**[q,r,K]

[a]Endocrinology Unit, Department of Clinical Sciences and Community Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy [b]Endocrine Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA [c]Biomedical Research Centre, University of East Anglia, Norwich Research Park, Norwich, UK [d]Pediatric Endocrinology Unit, Department of Public Health and Pediatric Sciences, University of Torino, Torino, Italy [e]Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics, University of Lübeck, Lübeck, Germany [f]Developmental Endocrinology Research Group, School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, UK [g]Italian Progressive Osseous Heteroplasia Association (IPOHA), Foggia, Italy [h]K20, French PHP and Related Disorders Patient Association, Jouars-Pontchartrain, France [i]APHP, Department of Medicine for Adolescents, Bicêtre Paris Saclay Hospital (HUPS), Le Kremlin-Bicetre, France [j]Institute of Human Genetics, Medical Faculty, RWTH Aachen University, Aachen, Germany [k]AEPHP, Spanish PHP and Related Disorders Patient Association, Almeria, Spain [l]Albright Center and Center for Rare Bone Disorders, Division of Pediatric Endocrinology and Diabetes, Connecticut Children's Medical Center, Farmington, CT, USA [m]Department of Pediatrics,

Guiomar Perez de Nanclares, Molecular (Epi)Genetics Laboratory, BioAraba Reseach Health Institute, Araba University Hospital-Txagorritxu, C/Jose Atxotegi s/n, ES–01009 Vitoria-Gasteiz (Spain), gnanclares@osakidetza.eus; Agnès Linglart, Reference Center for Rare Disorders of Calcium and Phosphate Metabolism, Platform of Expertise Paris-Saclay for Rare Diseases, Bicêtre Paris Saclay Hospital, 74 Avenue du Général Leclerc, FR–94270 Le Kremlin Bicêtre (France), agnes.linglart@aphp.fr.

M.B., D.M., L.S., and S.T. are co-second authors and equally contributed to this work. G.P.N. and A.L. are co-last and corresponding authors.

Author Contributions

G.P.N., G.M., and A.L. researched data for this article, contributed to discussion of the content, wrote this article, and reviewed and/or edited this paper before submission. M.B., D.M., L.S., S.T., S.F.A., R.B., T.C., G.D.F., G.D., T.E., F.M.E., A.G.R., E.L.G.-L., L.G., N.A.T.H., P.H., O.H., H.J., P.K., N.K., E.L.N., B.L., M.A.L., O.M., R.M, G.A.M.-M., M.M., P.M., A.P., R.P., L.R., R.R., A.R., V.S., A.H.S., E.M.S., C.S., S.T., P.W., and M.C.Z. contributed to discussion of the content and reviewed and/or edited this paper before submission. All of the authors agreed with the last version of this paper.

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University of Connecticut School of Medicine, Farmington, CT, USA [n]APHP, Department of Endocrinology, Cochin Hospital (HUPC), Paris, France [o]University of Paris Descartes, Sorbonne Paris Cité, Paris, France [p]Division of Endocrinology and Centre for Bone Quality, Department of Medicine, Leiden University Medical Center, Leiden, The Netherlands [q]INSERM U1185, Bicêtre Paris Sud – Paris Saclay University, Le Kremlin-Bicêtre, France [r]APHP, Reference Center for Rare Disorders of Calcium and Phosphate Metabolism, Platform of Expertise Paris-Saclay for Rare Diseases and Filière OSCAR, Bicêtre Paris Saclay Hospital (HUPS), Le Kremlin-Bicêtre, France [s]APHP, Department of Endocrinology and Reproductive Diseases, Bicêtre Paris Saclay Hospital (HUPS), Le Kremlin-Bicêtre, France [t]Acrodysostosis Support and Research patients' group, London, UK [u]APHP, Department of Odontology, Bretonneau Hospital (PNVS), Paris, France [v]Department of Endocrinology and Nutrition, La Paz University Hospital, Madrid, Spain [w]Department of Medicine, Autonomous University of Madrid (UAM), Madrid, Spain [x]Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain [y]Division of Endocrinology and Diabetes and Center for Bone Health, Children's Hospital of Philadelphia, Philadelphia, PA, USA [z]Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA [A]Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland [B]Osteometabolic Disorders Unit, Hormone and Molecular Genetics Laboratory (LIM/42), Endocrinology Division, Hospital das Clínicas HCFMUSP, Faculty of Medicine, University of Sao Paulo, Sao Paulo, Brazil [C]Department of Endocrinology, Hospital Infantil Universitario Niño Jesús, Hospital La Princesa Institute for Health Research (IIS La Princesa), Madrid, Spain [D]Department of Pediatrics, Autonomous University of Madrid (UAM), Madrid, Spain [E]CIBERobn, Instituto de Salud Carlos III, Madrid, Spain [F]Division of Endocrinology, Chiba Children's Hospital, Chiba, Japan [G]Department of Paediatric Endocrinology, Royal Manchester Children's Hospital, Manchester University NHS Foundation Trust, Manchester, UK [H]Molecular (Epi)Genetics Laboratory, BioAraba Research Health Institute, Araba University Hospital-Txagorritxu, Vitoria-Gasteiz, Spain [I]Department of Medicine, Mayo Clinic, Rochester, MN, USA [J]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark [K]APHP, Endocrinology and Diabetes for Children, Bicêtre Paris Saclay Hospital (HUPS), Le Kremlin-Bicêtre, France [L]Department of Endocrinology and Diabetes, Birmingham Children's Hospital, Birmingham, UK [M]Pediatric Endocrinology and Diabetes, Vanderbilt University Medical Center, Nashville, TN, USA [N]Departments of Orthopedic Surgery and Genetics, Center for Research in FOP and Related Disorders, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA [O]APHP, Service de Biochimie et Génétique Moléculaires, Hôpital Cochin, Paris, France [P]Department of Pediatrics, Division of Endocrinology and Diabetes, Marmara University, Istanbul, Turkey [Q]Department of Internal Medicine, Bone Center Erasmus MC – University Medical Center Rotterdam, Rotterdam, The Netherlands

Abstract

Patients affected by pseudohypoparathyroidism (PHP) or related disorders are characterized by physical findings that may include brachydactyly, a short stature, a stocky build, early-onset obesity, ectopic ossifications, and neurodevelopmental deficits, as well as hormonal resistance most prominently to parathyroid hormone (PTH). In addition to these alterations, patients may develop other hormonal resistances, leading to overt or subclinical hypothyroidism, hypogonadism

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and growth hormone (GH) deficiency, impaired growth without measurable evidence for hormonal abnormalities, type 2 diabetes, and skeletal issues with potentially severe limitation of mobility. PHP and related disorders are primarily clinical diagnoses. Given the variability of the clinical, radiological, and biochemical presentation, establishment of the molecular diagnosis is of critical importance for patients. It facilitates management, including prevention of complications, screening and treatment of endocrine deficits, supportive measures, and appropriate genetic counselling. Based on the first international consensus statement for these disorders, this article provides an updated and ready-to-use tool to help physicians and patients outlining relevant interventions and their timing. A life-long coordinated and multidisciplinary approach is recommended, starting as far as possible in early infancy and continuing throughout adulthood with an appropriate and timely transition from pediatric to adult care.

Keywords

Acrodysostosis; Bone disorders; Brachydactyly; Calcium and phosphate metabolism; Consensus; Diagnosis; Management; Ossification; Parathyroid hormone; Pseudohypoparathyroidism; Treatment

Introduction

Much progress has been made since 1942 when Albright et al. [1] described pseudohypoparathyroidism (PHP) as a novel disorder of hormone resistance in which hypocalcemia and hyperphosphatemia were due to a decreased responsiveness to parathyroid hormone (PTH). Patients also manifested an unusual appearance characterized by a short stature, brachydactyly, obesity with a round face, and heterotopic ossifications. This was known as Albright hereditary osteodystrophy (AHO). Initially, reports focused on clinical aspects, leading to the identification of a constellation of disorders associated with a similar spectrum of physical characteristics and neurocognitive and endocrine abnormalities which included the different subtypes of PHP (i.e., PHP type 1A due to maternal loss-of-function variants at the *GNAS* coding sequence [PHP1A], PHP type 1B due to methylation defect at the *GNAS* locus [PHP1B], pseudo-PHP [PPHP], and progressive osseous heteroplasia [POH]).

Today the term pseudohypoparathyroidism (OMIM 103580 for PHP1A, 603233 for PHP1B, and 612462 for PHP type 1C [PHP1C]) describes disorders that share biochemical characteristics of hypoparathyroidism, i.e., hypocalcemia and hyperphosphatemia, as a result of proximal tubular resistance to PTH. Some patients present with resistance to other hormones (such as thyroid-stimulating hormone [TSH] and/or gonadotropins, growth-hormone-releasing hormone, and calcitonin).

Patients with PHP1A, and rare PHP1B cases, manifest physical features of AHO due to defects in chondrocyte and osteoblast differentiation, early closure of growth plates, brachydactyly, a short stature, and development of ectopic ossifications. AHO typically develops during late childhood. Years after the description of PHP, Albright and et al. [1] described patients with some physical features of AHO despite appropriate PTH responsiveness. Albright et al. [1] originally termed this condition PPHP (OMIM 612463).

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We know today that POH (OMIM 166350) or osteoma cutis belongs to the same disease entity, with a variable extent of the heterotopic ossifications and brachydactyly. On the other side, PTH resistance in absence of the AHO phenotype is the main characteristic of most PHP1B patients [2]. Recent studies have further defined the phenotype of these related disorders including other associated features such as impaired intrauterine growth in PPHP [3], and early-onset obesity [4], frequent respiratory and ENT complications [5], delayed verbal [6] and nonverbal [7] milestones, and cognitive impairment [7], mainly in PHP1A.

Since the 1990s, PHP1A and PPHP have been known to be caused by heterozygous Gsα-inactivating pathogenic variants [8, 9]. It was subsequently shown that the disease phenotype associated with the variant depends on the alterations' maternal (PHP1A) or paternal (PPHP) [10]/POH [11] inheritance. The molecular mechanism leading to PHP1B was discovered in 2003. Patients affected with PHP1B present with methylation defects at the *GNAS* locus [12] (see Molecular Diagnosis). The term PHP type 1C was initially used for patients displaying a PHP1A phenotype yet a biochemical normal Gsα activity; the denomination should now be abandoned and patients should be referred to as PHP1A, as they carry maternally inherited inactivating pathogenic Gsα variants.

New biochemical and molecular techniques have uncovered that disorders similar to PHP, such as acrodysostosis (OMIM 101800) [13, 14], are due to different defects within various genes involved in the stimulatory G-protein-coupled receptor signaling pathway [15] (e.g., *GNAS* [2, 16, 17], *PRKAR1A* [14], *PDE4D* [13, 18], or *PDE3A* [19]). Today, molecular analyses can identify de novo or inherited genetic or epigenetic alterations in around 80–90% of patients with PHP or related disorders [20, 21] (Fig. 1).

Since publication of the original consensus statement for PHP and related disorders [22], new relevant findings have been published. Therefore, with the aim of disseminating and updating the international consensus statement, the 3 main investigators (A.L., G.M., and G.P.N.) together with 34 of the 37 experts collaborated on this shortened and updated paper.

The literature search was updated from December 18, 2016, to December 31, 2019, using the same key terms as in the previous version, leading to a total of over 1,000 articles.

The addition of the recently published evidence did not modify the content of the previously published recommendations but further strengthened the underlying background and experts' opinions and prompted us to develop a more concise and practical tool designed to help health care professionals involved in the management of patients with PHP and patients and their families.

Clinical Diagnosis and Management

PHP and the aforementioned disorders share a common defect in the cAMP signaling pathway downstream of the PTH/PTHrP receptor. Despite this unifying molecular umbrella, presentation and disease severity can 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) [23], early-onset

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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 a lack of recognition of the syndrome and associated features. Later in life, growth failure, brachydactyly, obesity, and/or hypocalcemia leading to neuromuscular symptoms or even seizures often leads 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, the family history.

The following major features should be present in order to diagnose a patient with PHP or a related disorder: 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, hypercalcitoninemia, hypogonadism, growth hormone (GH) deficiency, cognitive impairment, hearing impairment, craniosynostosis and neurosurgical features, tooth ankylosis, oligodontia, cataract and/or CNS calcifications, sleep apnea, ear infections, asthma, and restricted fetal growth (Fig. 2).

Once a clinical suspicion exists, 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 vs. 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 (Fig. 3). The use of genetic and 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, a correct diagnosis will guide appropriate management including prevention of complications, life-style adjustments, screening and treatment of endocrine deficits, and appropriate genetic counselling.

Sufficient prospective clinical trials and outcomes data in PHP and related disorders is lacking. Thus, management guidelines are mainly based on experts' consensus. We have summarized in this document (see below) and in Table 1 the principal multidisciplinary interventions that should take place during the follow-up of these patients.

Resistance to PTH

PTH resistance is the hallmark of PHP, found in 45–80% [24] of patients, particularly in those with PHP1A and 1B. It is defined by the association of hypocalcemia, hyperphosphatemia and elevated serum levels of PTH in the absence of vitamin D deficiency, abnormal magnesium levels, and/or renal insufficiency [22]. PTH resistance is usually absent at birth and develops over time [25]; in addition, diagnosis maybe difficult in the absence of one or several biochemical features, e.g., hypocalcemia or hyperphosphatemia [13, 18, 22, 26-28]. Typically, in children, symptoms appear during periods of rapid growth, most likely because of increased calcium and vitamin D requirements [29]. The screening and follow-up of PTH resistance should include measurement of PTH, 25-OH vitamin D, calcium, and phosphate every 3–6 months in

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children and at least yearly in adults. Monitoring should be more frequent in symptomatic individuals and during acute phases of growth, intercurrent illness, pregnancy, and breastfeeding, when dosage requirements for active vitamin D metabolites or analogs might change. Patients and/or their families should be taught to recognize clinical signs of hypocalcemia and hypercalcemia [22].

The management of severe symptomatic hypocalcemia does not differ from that of hypoparathyroidism [30]. However, treatment using activated forms of vitamin D combined with (in most cases) oral calcium supplementation should target levels of calcium and phosphorus within the normal range while avoiding hypercalciuria; PTH levels should be within mid-normal to up to 2 times the upper limit of normal as higher levels of PTH might have adverse effects on skeletal mineralization or on the growth plate and evolve towards tertiary hyperparathyroidism [31-34]. Regardless of the level of serum calcium, treatment with active vitamin D analogs should be considered when PTH levels reach more than twice the upper limit of normal. Calcium supplements should also be considered, depending on the calcium dietary intake. Normal levels of 25-OH vitamin D should be maintained for all patients with appropriate supplementation [22].

Patients with PHP and related disorders rarely develop hypercalciuria and/or nephrocalcinosis because of the preserved PTH sensitivity of the distal renal convoluted tubules [29, 35, 36]. However, episodes of nephrolithiasis have been seldom observed (unpubl. obs.) 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 [22, 30].

Chronic hypocalcemia with hyperphosphatemia can result in an elevated calcium × phosphate product, which can lead to ectopic calcification (not to be confused with the ectopic ossification of AHO that occurs independently of serum levels of calcium and phosphate). Intracranial calcifications of the basal ganglia resemble those occurring in Fahr syndrome due to pathogenic variants in the *SLC20A2* gene; note that patients with PHP may often have additional calcification of the cerebral white matter [37]. So far, brain calcifications have not been described in patients with PPHP or POH or those with an alteration in the *PRKAR1A* or *PDE4D* genes [13, 14, 38-41]. Ectopic depositions of calcium and phosphorus may occur in the eyes, leading to posterior subcapsular cataract or corneal opacities [41-45]. A brain CT scan is indicated only in the case of neurological manifestations, while systematic and regular ophthalmologic examination is recommended to diagnose or manage cataracts.

Finally, PHP is often associated with dental and oral features such as failure of tooth eruption, impaction of primary molars, hypodontia, enamel hypoplasia, malocclusion, gingival hyperplasia, and gingivitis with spontaneous bleeding and pain [46-49]. Regular dental reviews every 6–12 months are recommended, at least during childhood [22, 50].

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Ectopic Ossification

Ectopic ossifications are found in 100 and 80–100% of patients with POH and PPHP/AHO, respectively, in 30–70% of PHP1A patients, and very sporadically in those with PHP1B, while they have never been reported in patients with acrodysostosis [27, 51]. Ectopic ossifications should therefore be considered as a specific consequence of *GNAS* molecular alterations, especially when located on the paternal allele [52]; Gsα deficiency in mesenchymal stem cells favors de novo formation of extraskeletal islands of ectopic bone in dermis and subcutaneous fat [53, 54].

In contrast to what has been described in *Gnas* knock-out mouse models of AHO [55], and unlike fibrodysplasia ossificans progressiva (FOP), there is no scientific evidence that inflammation or traumatic events contribute to ectopic bone formation in *GNAS*-related conditions [56, 57]. This notwithstanding, ectopic bone formation often develops, in *GNAS* related disorders, in locations subjected to high pressure loads, such as the heel [58].

POH is defined by ossifications located in and extending towards connective tissues, muscles, tendons, and ligaments [11, 52, 57]. In contrast, ectopic bone formation remains superficial in osteoma cutis, PHP1A, PPHP, or AHO.

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 and it is contraindicated in case of suspicion of FOP.

Due to the rarity of these conditions, limited information is available about prognosis, and so far no effective treatments exist for the management or prevention of ectopic ossifications.

Cutaneous bony plaques should be investigated by careful clinical examination at each visit, especially in patients with pathogenic or probably pathogenic variants on the *GNAS* paternal allele (POH and PPHP). Patients and families should be instructed about self-examination. The location and size of the ossifications, involvement of joints and impairment of movement and bone growth, and evolution during puberty or rapid growth should be documented at each visit.

Imaging of ossifications should be performed using CT or MRI only in the case of painful or symptomatic lesions, if joint or organ function is being jeopardized, or when considering surgical excision.

Physical therapy and meticulous skin care are critical for the prevention of complications due to ectopic ossifications. Due to a high risk of recurrence, surgical excision should be limited to well-delimitated, superficial lesions causing pain and/or movement impairment [11, 22, 57]. In ossifications involving joints, immobilization, e.g., through casts, should be avoided to prevent ankyloses. No evidence supports the use of nonsteroidal anti-inflammatory drugs, bisphosphonates, or steroids in primary or perisurgical treatment of asymptomatic ectopic ossifications [22].

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Brachydactyly

Brachydactyly is not specific to PHP and related disorders. Affected patients display brachydactyly type E [59], with a high degree of variability in frequency and severity. Brachydactyly is found in the majority of patients with PHP1A and PPHP (70–80%), in few with PHP1B (15–33%), and in all patients with acrodysostosis [22] (Fig. 2).

Brachydactyly develops over time and might not be present or visible in early life, except in patients with acrodysostosis [14, 60]. Clinical and radiological examination of the hands and feet is important from early childhood onwards to establish the diagnosis. It may impair fine motor skills, such as handwriting [61]. In some patients occupational therapy and/or appropriate orthopedic devices, e.g., special shoes and orthopedic insoles, may be indicated [22].

Additional bone features, such as carpal tunnel syndrome [61], Madelung deformity [62], spinal stenosis [63], acro-osteolysis, phalangeal cone-shaped epiphyses, and craniosynostosis [64] have been described. Depending on the functional consequences, these skeletal manifestations may require a specific multidisciplinary evaluation and orthopedic corrective surgery [22].

Management of Growth and GH Deficiency

The majority of PHP1A and PPHP patients display adult short stature, 2.5 SD below the mean in average, despite having a normal length/height during childhood [3]. The short stature is even more pronounced in acrodysostosis, with the final height being on average −3.5 SD (−8.8 to −0.5 SD) [22]. Noticeably, most patients with a paternal *GNAS* pathogenic variant (i.e., patients with PPHP or POH) and patients with acrodysostosis show restricted fetal growth and are thus born SGA [22]. Intrauterine growth restriction, advanced bone maturation, an impaired pubertal growth spurt, and, in PHP1A, GH-releasing hormone resistance and consequently GH deficiency can contribute to the premature cessation of growth and a short stature in adulthood [3, 22]. Careful and regular monitoring of growth, skeletal maturation and GH secretion is therefore advised in all affected children, starting around the age of 3–6 years. Patients born SGA who do not demonstrate appropriate catch-up growth or patients showing a GH deficiency should be rapidly considered for treatment with rhGH [22]. As of today, there is insufficient evidence to establish the efficacy and safety of pubertal blockers to increase the final height in these patients [65]. In contrast to PHP1A and PPHP patients, and despite an enhanced growth velocity during infancy, PHP1B patients display adult heights similar to those of the general population [3, 66].

Obesity

Patients with PHP1A or PHP1B develop early-onset obesity, usually within the first 2 years of life; this may be the first and only symptom in many patients until the diagnosis is established during adolescence or adulthood [3, 4, 67, 68]. Several mechanisms may contribute to excessive acquisition and maintenance of fat mass, including a defect in the Gsα-dependent melanocortin signaling pathway (possibly responsible for the patients' hyperphagic trait [68, 69]), decreased resting energy expenditure compared to obese controls

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[68, 70, 71], low sympathetic nervous system activity, decreased lipolysis [72], and GH-releasing hormone resistance in the pituitary [73, 74]. Overall, we now know that obesity or overweight is associated with all types of PHP and related disorders [22], with the exception of POH, PPHP, and osteoma cutis [3, 52, 57, 75, 76]]. Once the diagnosis is made, BMI and eating behaviors should be regularly monitored. Patients, parents, and families should be provided with psychological support and educational programs, as early as possible, even in the presence of a normal BMI as a preventive strategy, also taking into account the low resting energy expenditure of these patients [3].

Sleep apnea, a well-known complication of obesity, has been reported to be more frequent in patients affected with PHP1A [77, 78] and may also be present in acrodysostosis [40]. Phenotypically, these patients present with round faces, a flattened nasal bridge, and/or maxillary hypoplasia [26, 50] which, combined with obesity, mechanically contributes to the development of sleep and respiratory disturbances [70, 77]. All patients with PHP and related disorders should therefore be screened for restless sleep, snoring, inattentiveness, and daytime somnolence and, if present, polysomnography is recommended.

Metabolic Syndrome

Decreased insulin sensitivity and type 2 diabetes are present in a large proportion of adult PHP1A patients and may not be solely related to obesity [79]. Postprandial hyperglycemia is common in children with PHP1A and PHP1B [71]. The lipid profile is not profoundly affected in PHP1A patients [69, 80]. Hypertension was reported in 1 study of PHP [81], yet the incidence of cardiovascular diseases was not increased in cohort studies conducted in Denmark [41, 80]. Other studies have failed to find an increased risk of hypertension compared to matched controls [69, 71, 79]. Overall, we propose inclusion of regular monitoring of blood pressure, lipid profile, and glucose metabolism parameters 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 and in 0–10% of patients with PPHP or POH, and it is rarely observed in patients with PHP1B and has a variable prevalence in patients with acrodysostosis [22]. Cognitive performance studies have been undertaken only in PHP1A and they have shown reduced scores in comparison to peers [6, 37, 82, 83], with an average IQ of 85.9 and a reduction of 21.5 IQ points below an unaffected sibling [7]. Patients with PHP1A have been found to have impaired executive function, delayed adaptive behavior skills, and increased rates of attention deficit hyperactivity disorder [7]. One retrospective review of developmental milestones showed a greater delay in language compared with gross motor skills, with and a tendency to improve during late childhood [6]. Neurological and neuropsychiatric manifestations can be linked to the function in addition to the role of Gsα in brain development [84], and other organic CNS alterations, including Chiari 1 malformation [85-87] or prolonged periods of hypocalcemia [83, 87] found in some patients. Patients with PHP and related disorders should be referred to a neuropsychologist for neurocognitive and/or behavioral assessment at diagnosis or at preschool age, especially patients with PHP1A and acrodysostosis due to *PDE4D*

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pathogenic variants mutations. Most patients will require specialized educational assistance [7].

TSH Resistance

TSH resistance is not as severe as PTH resistance due to partial Gsα imprinting in the thyroid tissue [88-90]. Most patients with PHP1A [51, 74] present elevated serum levels of TSH, a small thyroid gland, and normal or only mildly depressed serum levels of thyroid hormone. Elevated levels of TSH due to TSH resistance are often present at birth; some patients may be diagnosed through neonatal screening [22]. In contrast, PHP1B patients display TSH levels at the upper end of normal or mildly elevated levels [22]. TSH resistance is present in patients with acrodysostosis due to pathogenic variants at *PRKAR1A* but not in those at *PDE4D* [26, 27]. Despite a prompt diagnosis of hypothyroidism after birth and initiation of treatment, this does not seem to prevent motor or cognitive delay [82].

In children and adults, investigation, monitoring, and treatment objectives do not differ from other etiologies of hypothyroidism/subclinical hypothyroidism, including hypothyroidism related to TSH resistance [22, 91].

Alterations in Gonadal Function

Gonadal Function and Puberty

Resistance to gonadotrophins is more subtle than resistance to other hormones such as PTH and TSH. This suggests that PHP1A patients display only a partial resistance to gonadotropins [22, 92]. Clinically, patients may present with menstrual irregularities in girls [92], cryptorchidism in boys [93 and experts' experience], and a blunted or absent pubertal growth spurt in adolescents [3] with PHP1A. PHP1B and PPHP patients seem to have a normal gonadal function [94], while a variable resistance to gonadotropins has been described in patients with acrodysostosis and pathogenic variants in the *PRKAR1A* gene [26].

In children with PHP or related disorders, Tanner staging of sexual maturation and testicular descent and location should be regularly assessed. As skeletal maturation is typically advanced in these children, bone age should be radiographically determined. 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 standard recommendations [22].

Fertility and Pregnancy

Assisted and spontaneous pregnancies have been reported in women with PHP and related disorders [22, 92, 95]. Men with PHP1A have also fathered children. For disease transmission risks, see Molecular Diagnosis.

In the case of hypocalcemia and/or hypothyroidism, pregnant women with PHP and related disorders should be monitored following the international guidelines for any pregnancy associated with these disturbances. Vaginal delivery may be contraindicated due to the

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reduced pelvic size and the decreased range of motion of the hips due to local ossifications [22]. The newborn should be evaluated for the presence of skin ossifications and levels of TSH, calcium, and phosphorus. Breastfeeding is not contraindicated, but close follow-up and clinical monitoring of the baby are advised [22].

Menopause and Osteoporosis

Although patients with PHP do have several potential risk factors for bone fragility, they do not generally demonstrate evidence for a decreased bone density and/or an increased fracture risk [41,96, 97]; in this context, routine DXA measurement is not indicated [22]. On the other hand, further investigation is required should a diagnosis of osteoporosis be suspected, for instance after sustaining a low trauma fracture or in the case of skeleton unloading (e.g., joint ankyloses secondary to aberrant ossification). Patients should then be screened for potential secondary causes of bone loss such as vitamin D deficiency, hypogonadism, or GH deficiency, and all efforts should be made to correct these before treating the osteoporosis if still required according to national and international standard recommendations.

Other Hormone Resistances

Elevated calcitonin levels, most likely due to calcitonin resistance, have been reported in PHP1A [98, 99], PHP1B, and acrodysostosis patients with PRKAR1A pathogenic variants [14]. They may be used to support the diagnosis of PHP and related disorders. Additional resistance to hormones that mediate their actions through Gsα-coupled receptors has also been previously reported, although the clinical relevance of these abnormalities remains to be established [100]. Screening of additional hormone resistances, and calcitonin measurement, is not recommended in patients with PHP and related disorders, except for diagnostic purposes [22].

Molecular Diagnosis

The main subtypes of PHP and related disorders are caused by de novo or autosomal dominant inherited inactivating genetic pathogenic variants within the genes of the PTH/PTHrP signaling pathway [15] or by epigenetic alterations at the *GNAS* locus. The *GNAS* locus presents 4 distinct differentially methylated regions (DMR; online suppl. Fig. 1, see www.karger.com/doi/10.1159/000508985 for all online suppl. material): the paternally methylated region (*GNAS-NESP:TSS-DMR*) and 3 maternally methylated regions (*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 single-nucleotide and copy number variants [8, 9, 22]. When the pathogenic variants are on the paternal allele, the outcome is mainly PPHP but it can also include osteoma cutis or POH [11, 22]. Single-nucleotide variants can be easily detected by sequence analysis, whereas genomic rearrangements can be detected by quantitative methods [101]. Determination of the affected allele in de novo cases is becoming relevant, as a few PPHP patients may also develop hormone resistance [102]. Genetic counseling is critical for PHP and related disorders; patients with *GNAS* genetic variants have a 50% chance of transmitting the molecular defect. Depending on parental sex, their offspring will

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develop PPHP, osteoma cutis, or POH (when the transmitting patient is male) or PHP1A (when the transmitting patient is female).

Loss of methylation at *GNAS A/B*:TSS-DMR is detected in all patients with PHP1B [22, 103]. When it is the only affected DMR (15–20% of PHP1B cases) [21], it is most often the consequence of an alteration in the maternal allele of *cis*-acting control elements within *STX16* [12]. 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 4 DMR [22]. 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) [12].

On the other hand, sporadic PHP1B is often associated with methylation defects at 2 or more DMR, in addition to *GNAS A/B*:TSS-DMR, with no identified underlying genetic mechanism [104]. In around 8–10% [21, 105] of these sporadic cases, the methylation anomalies are caused by paternal uniparental disomy of the chromosomal region comprising *GNAS* (UPD[20q]pat) [22, 106]. In these patients, the recurrence and transmission risks are expected to be similar to those of the general population.

Although *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 simultaneously of methylation defects at the different GNAS DMR as well as *STX16* and *NESP/AS* deletions and deletions encompassing *GNAS* [107].

Paternal uniparental isodisomy can be analyzed either by microsatellite (short tandem repeats) typing or SNP array.

In brief, in individuals with a suspected diagnosis of PHP, molecular diagnosis must include DNA sequence, methylation, and CNV 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* [13, 14, 18], so they can be easily detected by sequencing. They mostly occur de novo [22], 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 children.

Conclusions

Patients with PHP and related disorders may display a highly heterogeneous and progressive clinical picture over their life span from infancy to adulthood, which renders a life-long multidisciplinary approach mandatory. Each of the many clinical aspects and potential complications of the disease should be managed by health care professionals with expertise in these disorders, preferably 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 to establish a correct molecular diagnosis, which is often difficult and time

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

Following up on the recent publication of the first international consensus statement on these disorders, this article provides an updated, concise, 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 the management of these patients, there is an urgent need to implement registries with large cohorts of patients, to better understand the natural history of PHP and related disorders, to identify the intersections as well as the specificities of these clinically heterogeneous but closely related diseases, and, last but not least, to enable the development of novel disease-specific therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

The COST action BM1208 (European Network for Human Congenital Imprinting Disorders, http://www.imprinting-disorders.eu), the European Reference Network on Rare Endocrine Conditions (ENDO-ERN), the European Reference Network on Rare Bone Disorders (BOND-ERN), the European Calcified Tissue Society (ECTS), the Asian Pacific Pediatric Endocrine Society (APPES), the European Society of Human Genetics (ESHG), the Pediatric Endocrine Society (PES), the European Society of Endocrinology (ESE), and the European Society for Paediatric Endocrinology (ESPE) endorsed the first consensus statement on PHP and related disorders.

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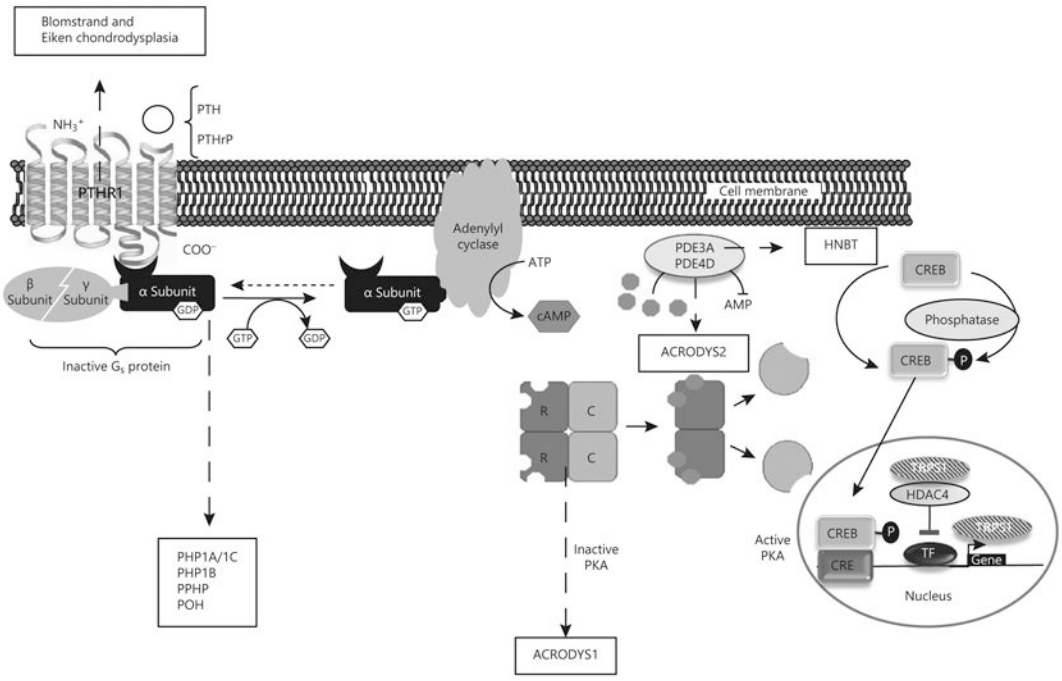

Fig. 1.

Molecular defects in the PTH-PTHrP signaling pathway in PHP and related disorders. The main clinical features of PHP and related disorders are due to molecular defects within the PTH-PTHrP signaling pathway, with the exception, perhaps, of ectopic ossification. Some of the clinical features result from the impaired signaling of other GPCR such as TSHR. The diseases caused by alterations at the genes codifying the indicated proteins are shown within square boxes. PTHR1, PTH/PTHrP receptor type 1; G protein, trimers α, β, and γ; PKA, tetramers R (regulatory subunit 1A; dark grey) and C (catalytic subunit; light grey); HTNB, autosomal dominant hypertension and brachydactyly type E syndrome; TF, transcription factor. Phosphodiesterases: ovals (PDE4D and PDE3A). cAMP: grey diamond.

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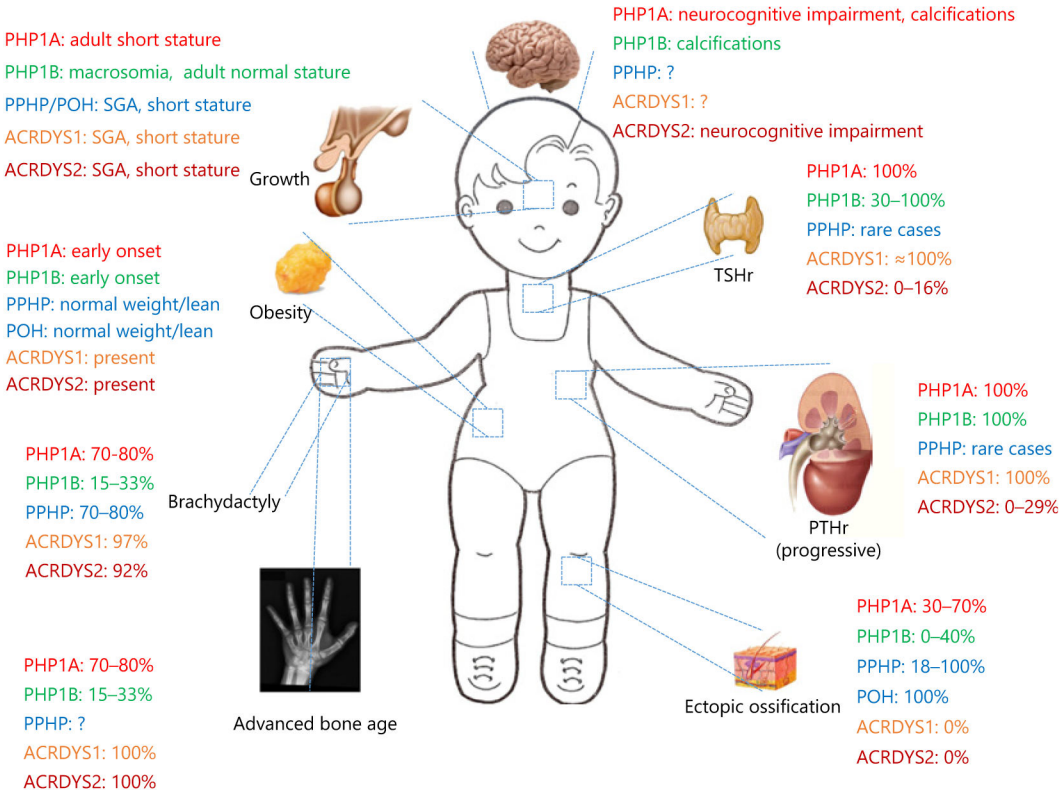

Fig. 2.

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. ACRDYS1, acrodysostosis due to a pathogenic variant in *PRKAR1A*; ACRDYS2, acrodysostosis due to alterations in *PDE4D*.

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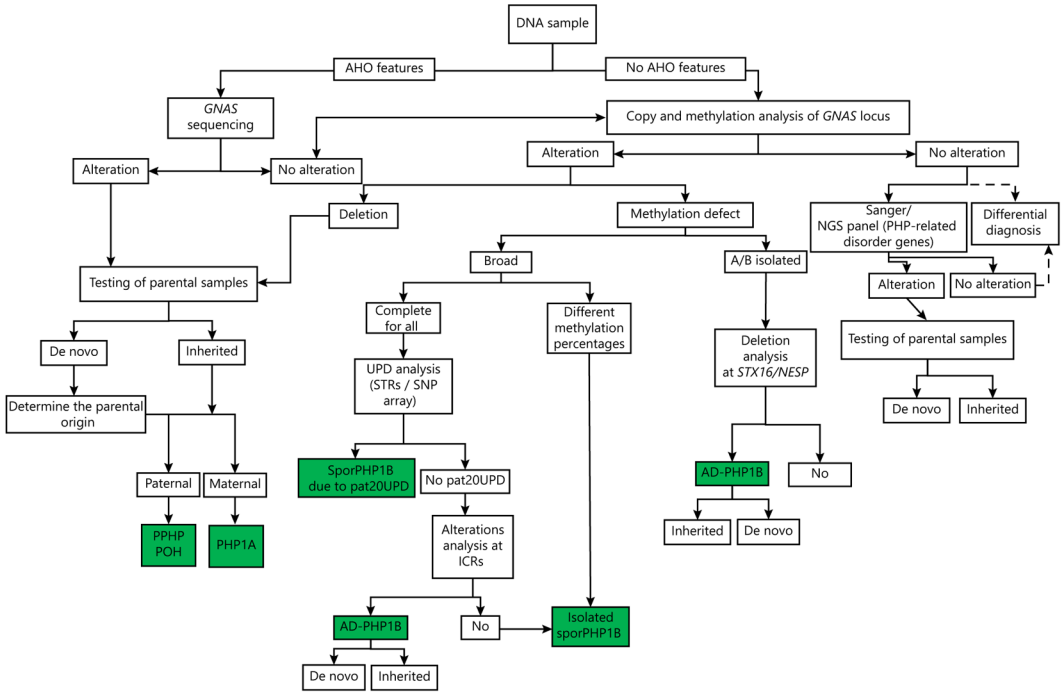

Fig. 3.

Molecular algorithm for confirmation of the diagnosis of PHP and related disorders. If patients present with AHO, genetic alterations at *GNAS* should be studied, including point variants (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 4 DMR, paternal uniparental disomy of chromosome 20 (UPD[20q] pat) should be screened for; in the 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 (i.e., 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; STR, short tandem repeats (microsatellites); UPD, uniparental disomy; WES, whole exome sequencing; WGS, whole genome sequencing; ICR, imprinting control region; VUS, variant of unknown significance.

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Table 1.

Summary of the main interventions during the follow-up of patients with PHP and related disorders

Action point	Infancy (newborn to 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
Psychosocial evaluation[a]	N/A	✓	S	S
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
Pubertal development	N/A	N/A	✓(biochemistry if delayed)	N/A
Fertility and sexual function	N/A	N/A		✓
Blood pressure	N/A	✓[b]	✓	✓
Biochemical analyses				
Calcium-phosphorus metabolism	✓	✓	✓	✓
Renal function	✓	✓	✓	✓
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	✓[c]	✓[c]	✓	✓[c]

Adapted from Mantovani et al. [23]. ✓, to be performed at diagnosis of PHP and related disorders and annually thereafter; S, subjective (by history and physical examination); N/A, not applicable.

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[a] Refers to social interactions and relations to peers.

[b] At least 1 time year, with an appropriate sized cuff.

[c] Annually in case of persistent hypercalciuria or nephrocalcinosis.