Diagnosis and Management of Pseudohypoparathyroidism and related Disorders: First International Consensus Statement

Giovanna Mantovani*, Murat Bastepe**, David Monk**, Luisa de Sanctis**, Susanne Thiele**, Alessia Usardi**, Faisal Ahmed, Roberto Bufo, Timothée Choplin, Gianpaolo DeFilippo, Guillemette Devernois, Thomas Eggermann, Francesca M. Elli, Kathleen Freson, Aurora García Ramirez, Emily Germain-Lee, Lionel Groussin, Neveen Hamdy, Patrick Hanna, Olaf Hiort, Harald Jüppner, Peter Kamenický, Nina Knight, Marie-Laure Kottler, Elvire Le Norcy, Beatriz Lecumberri, Michael A. Levine, Outi Mäkitie, Regina Martin, Gabriel Ángel Martos-Moreno, Masanori Minagawa, Philip Murray, Arrate Pereda, Robert Pignolo, Lars Rejnmark, Rebecca Rodado, Anya Rothenbuhler, Vrinda Saraff, Ashley Shoemaker, Eileen M. Shore, Caroline Silve, Serap Turan, Philip Woods, M. Carola Zillikens, **Guiomar Perez de Nanclares*, Agnès Linglart***

Acknowledgement: This consensus statement and the series of consensus meetings were supported by funds from the COST action BM1208 on imprinting disorders (www.imprinting-disorders.eu), the European Society for Paediatric Endocrinology (ESPE), and the European Society for Endocrinology (ESE). Travel costs and housing of the representatives of the Asian Pacific Paediatric Endocrine Society (APPES) and of the Pediatric Endocrine Society (PES) were supported by their societies. We received no funding from pharmaceutical companies.

Conclusion

- **The consensus statement covers recommendations for the clinical and molecular diagnosis, as well as the management of patients with pseudohypoparathyroidism (PHP) and related disorders.**
- **A coordinated and multidisciplinary approach from infancy through adulthood should help us to improve the care of patients affected by these rare disorders.**

Introduction

The G protein-Gsalpha-cAMP-protein kinase A-signaling pathway is one of the most important signaling pathway in human beings. Disruption of this pathway is caused by different gene mutations and leads to PHP and related disorders. These include the PHP-subtypes, such as PHP type 1A (PHP1A), Pseudo-PHP (PPHP), PHP type 1B (PHP1B), progressive osseous heteroplasia (POH), and acrodysostosis type 1 and 2 (ACRODYS1 und ACRODYS2).

The presentation and severity of clinical features vary between affected individuals with considerable overlap between the different types (see fig. 1). Clinical features include short bones, short stature, advanced bone age, a stocky build, early-onset obesity, and ectopic ossifications, as well as endocrine defects that often include resistance to PTH and TSH. A specific diagnosis is often delayed due to lack of recognitions of the syndrome and associated features and there is a lack on standardized guidelines for clinical diagnosis, molecular diagnosis, and management on these patient group.

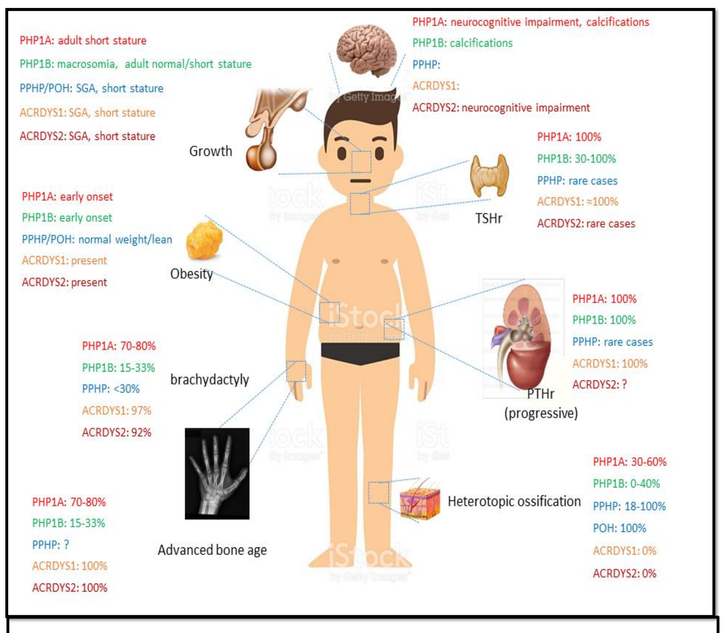


Fig. 1 Manifestation of PHP and related disorders. PTHr: PTH resistance, TSHr: TSH resistance

Methods

Thirty-seven participants from thirteen countries were invited to participate in the development of this consensus statement, based on their publication results and international accepted expertise.

Experts included representatives from six international societies (ECTS, APPES, ESHG, PES, ESE and ESPE), two European reference networks (ENDO-ERN, BOND-ERN) and a European network on imprinting disorders (COST BMI208); further, from patient support groups (AEPHP, K20, ACRODYS group, IPOHA).

A comprehensive literature search was conducted including articles published from January 1990 through December 2016. We reviewed over 800 articles in three working groups (clinical diagnosis, molecular diagnosis and management). The preparation for the consensus took over 24 months and included two pre-meetings.

Voting: A: evidence or general agreement allows full agreement to the recommendation, B is in favor, C is weak, D there is not enough evidence or general agreement to agree with the recommendation. If the majority was D, the recommendation was not accepted. Proportion of votes received by the option with the most votes, the strength of the recommendations was recorded as follows: +26-49% of votes, ++50-69, ++>=70. The representatives of the patient support groups took part on the discussions, but not on the voting.

Results

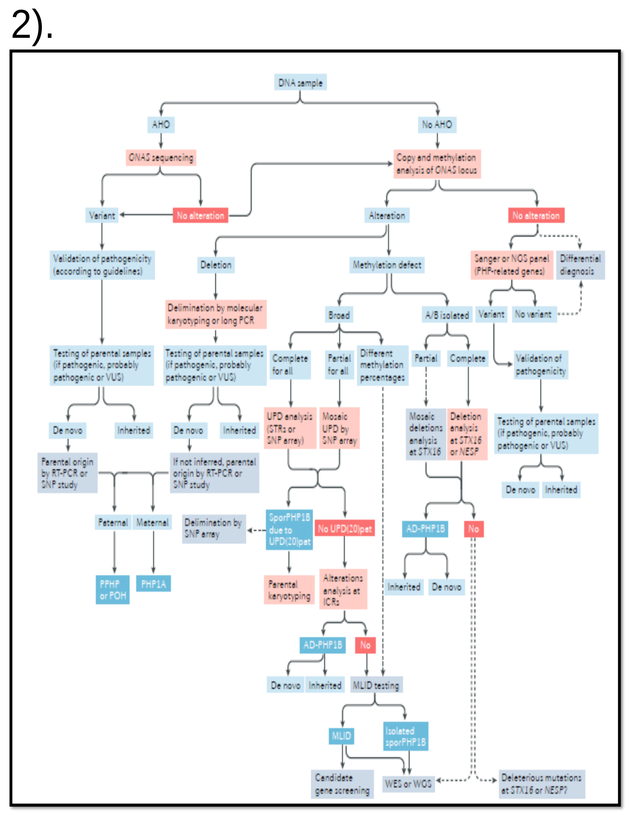
Working group 1 (Clinical diagnosis)*

- The diagnosis of PHP should be based on clinical and biochemical characteristics, which will vary depending on the age of the patients an, in some cases, on the family history (A+++).
- The diagnosis of Albright hereditary Osteodystrophy should be based on the two major criteria: brachydactyly type E and short stature by adulthood (relative to the height of the unaffected parent). Additional criteria are: stocky build, round face, obesity, and ectopic ossifications (A++).
- The major criteria for PHP and related disorders are: PTH resistance, and/or subcutaneous ossifications (that can include deeper ossifications), and/or early-onset obesity and/or AHO alone (A+++).
- The classification of PHP and related disorders should be amended to include a common pathophysiological framework and a molecular genetic classification.

Working group 2 (Molecular diagnosis)

The clinical and laboratory diagnosis should be confirmed by a molecular genetic analysis (see fig. 2).

Fig. 2 Molecular algorithm for the confirmation of diagnosis of PHP and related disorders. If patients present with AHO, genetic alterations at *GNAS* should be studied, including point mutations (sequencing) and genomic rearrangements (such as MLPA and aCGH). Once the variant is found, ist pathogenicity should be confirmed and when possible, the parental origin should be determined. In the absence of AHO, epigenetic alterations should be analysed first. According to the results of the methylation status, further tests are needed to reach the final diagnosis.



Working group 3 (Management of patients)

Patients should be screened at diagnosis and during follow-up for specific features, such as PTH resistance, TSH resistance, growth hormone deficiency, hypogonadism, skeletal deformities, oral health, weight gain, glucose intolerance of type 2 diabetes and hypertension, as well as subcutaneous and/or deeper ectopic ossifications and neurocognitive impairment. See ref. 2 (*Nature reviewsEndocrinology 2018)* for details.

* We developed 14 recommendations in WG1, 13 in WG2 and 40 in WG3. Here we present only a very small part of our results.

Reference

- From pseudohypoparathyroidism to inactivation PTH/PTHrP signalling disorders (iPPSD), a novel classification proposed by the EuroPHP network. *Euro J Endocrinol 2016* Dec; 175(6): 1-17
- Diagnosis and management of pseudohypoparathyroidism and related disorders: first international consensus statement. *Nature Reviews Endocrinology* 2018 Aug;14(8):476-500