https://doi.org/10.15446/cr.v8n2.105381

HYPERPARATHYROIDISM, HYPOPARATHYROIDISM, AND PSEUDOHYPOPARATHYROIDISM

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Received: 09/04/2022 **Accepted:** 29/06/2022

EDITORIAL

Calcium and phosphorus metabolism disorders are very frequent, and their identification may appear simple since measuring calcium (Ca), phosphorus (P), and parathormone (PTH) levels allows determining, in general, the underlying disease (1). Table 1 summarizes the most common findings concerning Ca, P, and PTH levels in relation to the main parathyroid diseases.

Table 1 Basic biochemical tests done to detect parathyroid hormone disorders.

Parathormone and calcium and phosphorus metabolism disorders	Calcium	Phosphorus	Parathormone
Primary hyperparathyroidism	Elevated	Decreased	Elevated
Secondary hyperparathyroidism	Normal-Low	Variable	Elevated
Hypoparathyroidism	Low	Elevated	Decreased
Pseudohypoparathyroidism	Low	Elevated	Elevated

Source: Own elaboration.

However, calcium and phosphorus metabolism is complex, and diagnosing a parathyroid disease always requires a systematic approach (2). This complexity stems from the fact that this metabolism involves various organs and hormones. Consequently, any change in Ca, P, or PTH levels should be thoroughly evaluated in order to analyze multiple serum and urinary parameters and thus arrive at a correct diagnosis (3-6).

The finding of elevated PTH levels in the presence of normal serum calcium levels (normocalcemic hyperparathyroidism) is frequent and a diagnostic challenge, as the differential diagnoses of normocalcemic hyperparathyroidism include common causes of secondary hyperparathyroidism such as renal disorders, low calcium or vitamin D intake, digestive disorders, and reactions to drug therapy, among others.

Pseudohypoparathyroidism (PHP) is a rare metabolic disease usually accompanied by hypocalcemia and hyperphosphatemia, that is often diagnosed in childhood or youth (7) and encompasses a group of diseases characterized by hypocalcemia, hyperphosphatemia, and target organ resistance to PTH, resulting in elevated PTH levels. This group of diseases has a common denominator: genetic and/or epigenetic alterations in the *GNAS* gene, which encodes the alpha subunit of the heterotrimeric stimulating protein G (Gsα) (8,9).

PHP has been classified into five different types: 1a, 1b, 1c, 2, and pseudo-pseudohypoparathyroidism (PPHP). However, diagnosing this condition is challenging and many cases are difficult to categorize due to clinical variability and the lack of *in vitro* complementation assays; furthermore, entities that may clinically overlap, such as acrodysostosis and progressive osseous heteroplasia, are not included in this classification (9).

Patients with PHP1a have phenotypic features of Albright hereditary osteodystrophy (AHO), including round face, short stature, brachydactyly, and subcutaneous ossifications, as well as resistance to PTH and other hormones with reduced Gsα activity (9). AHO is uncommon in PHP1b patients, and PTH resistance occurs only in the kidneys. Cases of AHO and PTH resistance with epigenetic defects, rather than Gs mutations, have been identified, with clinical and molecular overlap between PHP1a and PHP1b. Patients with PHP1c have multiple hormone resistances, but Gs activity is normal, and this type of PHP is defined as a variant of PHP1a in most classifications.

On the other hand, patients with PHP2 have a normal urinary cyclic adenosine monophosphate response to PTH; in addition, this variant also involves low Ca and high P levels in blood, and the genetic abnormality that causes it is unknown (9). Finally, PPHP is defined as the presence of phenotypic characteristics of AHO, decreased Gsα activity, and absence of PTH resistance. Subcutaneous ossifications (in the form of osteoma cutis or bone plaques) are also frequent in this type of PHP, and mild resistance to thyroid-stimulating hormone may occur in some cases (9).

The current issue of Case Reports presents the case of a 20-year-old diagnosed with PHP1a (10). This case report discusses factors that could have raised the suspicion of PHP, such as early-onset hypothyroidism, dysmorphic features of the patient, and the appearance of hypocalcemia with elevated PTH at puberty.

In this patient, medical history, physical examination, and laboratory and imaging test findings led the authors to request a DNA test for *GNAS* mutation due to the suspicion of PHP1a, confirming the diagnosis. This case also highlights the fact that no genetic alterations were observed among first-degree relatives and that, after starting treatment with calcium carbonate, calcitriol and aluminum hydroxide and adjusting the dose of levothyroxine, the patient had a favorable course (10).

PHP and its related diseases have a highly variable clinical expression and, therefore, their diagnosis may be delayed and not achieved until adulthood. PHP is a rare and probably underdiagnosed disease that should always be considered in the differential diagnosis of normo/hypocalcemia with elevated PTH levels.

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