

Management of Pseudohypoparathyroidism

Manejo del Pseudohipoparatiroidismo

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Abstract

Pseudohypoparathyroidism (PHP), now reclassified under the umbrella term inactivating PTH/PTHrP signaling disorder (iPPSD), is a rare endocrine disorder characterized by resistance to the parathyroid hormone (PTH), leading to hypocalcemia and hyperphosphatemia despite elevated PTH levels. This condition results from genetic mutations affecting the *GNAS* gene, which encodes the stimulatory G protein alpha subunit (*Gsa*) as well as methylation alterations at the various DMRs located at *GNAS* locus that involve a lower expression of *Gsa*. The disorder manifests through a range of endocrine, skeletal, metabolic, and neurocognitive abnormalities that significantly impact patients' quality of life. This review provides a comprehensive overview of the classification, pathophysiology, diagnosis, and current management strategies for iPPSD, emphasizing the importance of a multidisciplinary approach in optimizing clinical outcomes.

Introduction

Pseudohypoparathyroidism (PHP) was first described by Albright in 1942 as a disorder affecting calcium-phosphate metabolism due to impaired

PTH signaling. It encompasses a group of rare conditions characterized by resistance to PTH, leading to biochemical imbalances such as hypocalcemia and hyperphosphatemia. Apart from these metabolic disturbances, PHP is associated with resistance to multiple hormones, skeletal abnormalities, and neurocognitive deficits. The complex nature of this condition requires careful diagnostic evaluation and long-term management strategies⁽¹⁾. The newly proposed classification of inactivating PTH/PTHrP signaling disorder (iPPSD), developed by the European EuroPHP network, provides a more precise framework for understanding the pathophysiology and clinical spectrum of these disorders. It is based on clinical, biochemical, and genetic criteria, with major and minor diagnostic features^(2,3). At least one major criterion, from PTH resistance, ectopic ossifications, or brachydactyly type E, is required for diagnosis. Additionally, minor criteria provide supporting evidence, requiring at least two minor or one major criterion. These include TSH resistance, other hormone resistance, short stature and/or obesity, cognitive or neurodevelopmental impairment, and facial dysmorphism. This classification ensures a more comprehensive and standardized diagnosis of iPPSD.

Presentation of pseudohypoparathyroidism

PHP encompasses a spectrum of phenotypic features, including Albright's hereditary osteodystrophy (AHO), which manifests as short stature, brachydactyly, round face, and ectopic ossifications. Additional endocrine resistance, particularly to TSH, is common in PHP type 1A (PHP1A or iPPSD2mat), but is less frequent in other

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types. Biochemically, patients exhibit low serum calcium, elevated phosphate, and elevated PTH, with some individuals also displaying resistance to other hormones such as TSH, gonadotropins, and GHRH. Radiologically, the disorder is associated with skeletal abnormalities, including premature epiphyseal closure, shortening of the metacarpals (brachydactyly type E), and variable degrees of ectopic ossifications, which in severe cases may extend into connective tissues and muscles, restrict mobility and cause significant discomfort. Patients may present with intracranial calcifications, particularly in basal ganglia, resembling Fahr's syndrome with an incidence of up to 72% in some cohorts. Imaging techniques such as CT and MRI are useful in detecting these lesions, even in asymptomatic patients⁽⁴⁾. Growth and pubertal abnormalities are frequently observed, including short stature due to early epiphyseal closure with/without growth hormone (GH) deficiency. Cognitive and behavioral impairments including intellectual disability, executive dysfunction, and increased prevalence of ADHD affect a subset of patients, and require supportive interventions⁽⁵⁾. A distinctive feature of iPPSD, particularly in iPPSD2mat/PHP1A, is early-onset obesity that often develops during infancy. Studies suggest that this obesity results from reduced resting energy expenditure (REE) rather than increased caloric intake, differentiating it from common obesity. Dysfunction in hypothalamic melanocortin signaling has been implicated in the impaired regulation of energy homeostasis⁽⁶⁾.

The variable expressivity and phenotypic overlap among PHP subtypes necessitate genetic and epigenetic analysis for accurate diagnosis and classification.

Diagnosis

The diagnosis of iPPSD relies on a combination of clinical, biochemical, and genetic findings. Key diagnostic criteria include the evaluation of biochemical markers that may show serum calcium, elevated phosphate, and high PTH levels, with normal vitamin D, and of radiographic features showing evidence of brachydactyly and ectopic ossifications. Genetic diagnosis of iPPSD is essential for accurate classification, management, and genetic counseling. Early diagnosis has been demonstrated to be crucial for preventing complications and undertaking appropriate treatment⁽¹⁾. iPPSD disorders primarily result from molecular defects affecting the *GNAS* gene, which encodes the alpha subunit of the stimulatory G protein (G α) involved in PTH signal transduction. Maternal iPPSD2 (or PHP1A) is caused by maternally inherited inactivating variants in the *GNAS* gene, whereas paternal inheritance is associated with pseudopseudohypoparathyroidism (PPHP) or

progressive osseous heteroplasia (POH) or paternal iPPSD2. Meanwhile, iPPSD3 (or PHP1B) is associated with epigenetic alterations at the *GNAS* locus, leading to defective imprinting and methylation changes, and particularly loss of methylation in the A/B differentially methylated region (DMR, *GNAS* A/B:TSS-DMR). Molecular testing should therefore include sequencing of the *GNAS* gene, methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) to detect epigenetic changes, and SNP array analysis to identify uniparental disomy (UPD) when this is suspected. Other genes implicated in iPPSD include *PRKAR1A*, *PDE4D*, and *PDE3A*, which have been described in overlapping phenotypes such as acrodysostosis. Given the phenotypic overlap between different iPPSD subtypes, integrating genetic, epigenetic, and biochemical testing is crucial for establishing an accurate diagnosis and guiding appropriate management^(2,7).

Management

The management of hormone resistance in iPPSD primarily involves targeted hormonal substitution to correct metabolic imbalances and prevent complications. Treatment of PTH resistance typically consists of active vitamin D analogs such as calcitriol or alfacalcidol, combined with calcium supplementation to maintain serum calcium within the normal range while minimizing hypercalciuria and nephrocalcinosis. Recent guidelines emphasize that serum calcium should be maintained at the upper-normal limit to mitigate excessive PTH secretion and prevent tertiary hyperparathyroidism^(8,9). TSH resistance, frequently observed in iPPSD2mat/PHP1A and some iPPSD3/PHP1B, manifests as elevated TSH with normal or slightly reduced free T4 levels. Although many patients exhibit mild resistance, some require levothyroxine supplementation to maintain euthyroidism and support normal growth and neurodevelopment. Levothyroxine dosing in iPPSD is often higher than in primary hypothyroidism due to partial TSH insensitivity, and treatment should be tailored based on free T4 rather than TSH levels alone⁽⁸⁾. Regular biochemical monitoring, including serum calcium, phosphate, PTH, urinary calcium excretion, and thyroid function tests, is essential for optimizing therapy and preventing long-term complications. Growth hormone (GH) therapy has been shown to significantly improve growth velocity and final adult height in patients with iPPSD2/PHP1A presenting GH deficiency or short stature. A multicenter study demonstrated that recombinant human GH (rhGH) therapy led to a height gain of 0.7 SDS after one year and 1.5 SDS after three years, with a final adult height improvement of 1.9 SDS compared to untreated individuals. Importantly,

rhGH therapy did not significantly alter BMI, suggesting that weight management should be addressed separately⁽¹⁰⁾. Given these benefits, screening for GH deficiency in iPPSD2/PHP1A should be routine, and treatment should be considered at an early stage to optimize growth outcomes. Management of obesity is complex. A structured low-calorie diet focusing on nutrient-dense foods is recommended. Physical activity programs should be tailored to individual abilities, emphasizing metabolic benefits rather than rapid weight loss. Pharmacological interventions may be considered, such as metformin which has shown promise in improving insulin sensitivity and mitigating weight gain in some individuals^(11–13). In severe cases of morbid obesity unresponsive to medical interventions, bariatric surgery, such as a Roux-en-Y gastric bypass, may be considered, though long-term metabolic risks warrant careful evaluation. Emerging treatments targeting hypothalamic MC4R signaling are under investigation.

The biggest challenge in managing iPPSD is the treatment of ossifications. Except for the very limited and painful ossifications, surgery should be avoided. So far, there is no efficient treatment to reduce the ectopic ossification process. Sodium thiosulfate is currently under evaluation in clinical trials.

A multidisciplinary approach involving endocrinologists, nephrologists, and dietitians is crucial for comprehensive management and individualized treatment adjustments.

Futures directions

Advances in molecular medicine hold promise for targeted therapies that address the underlying genetic and epigenetic defects in iPPSD. Gene therapy and novel pharmacological interventions are being explored to improve treatment efficacy. Continued research and patient registries will be instrumental in refining clinical guidelines and therapeutic strategies.

Conclusion

The reclassification of PHP as iPPSD provides a more comprehensive and clinically relevant framework for diagnosis and treatment. Early recognition, precise diagnosis, and a tailored therapeutic approach are essential for optimizing patient outcomes. The integration of a multidisciplinary care model enhances disease management, and improves quality of life for affected individuals. Ongoing research will pave the way for innovative treatments

which may offer more effective and personalized care for patients with iPPSD.

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