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EDITORIAL

Wind of change in pseudohypoparathyroidism and related disorders: New classification and first international management consensus

Vientos de cambio en pseudohipoparatiroidismo y enfermedades relacionadas: nueva clasificación y primer consenso internacional

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The first description of patients affected with pseudohypoparathyroidism (PHP) dates back to 1942, when Fuller Albright and colleagues reported some patients that showed significantly reduced levels of plasmatic calcium with hyperphosphatemia associated with raised serum parathyroid hormone (PTH) levels and normal renal function, introducing, for the first time, the concept of end-organ resistance to a hormone. These individuals also displayed a clinical phenotype characterized by short stature, obesity, rounded face and brachydactyly, that was referred to as Albright's hereditary osteodystrophy (AHO).[1]

In the following years, the substantial increase in the research on this disease allowed the identification of different subtypes of PHP and additional clinical signs, such as ectopic subcutaneous ossifications and cognitive abnormalities in varying degrees, as well as the underlying pathophysiologic mechanism: a defective activation of the cAMP signal transduction pathway by PTH secondary to molecular defects affecting the alpha subunit of the stimulatory G protein (Gsα).[2–6] The discovery, in 1990, of inactivating mutations in *GNAS* (the gene encoding for Gsα) in patients with signs of AHO and with/without distinct hormone resistances (PHP1A and PPHP, respectively) can be considered a milestone in the study of this disease.[7,8]

Further molecular studies demonstrated that Gsα was predominantly maternally expressed in specific human tissues, including proximal renal tubules, pituitary, gonads, and thyroid. This differential tissue expression according to the parental origin of the allele (genomic imprinting) explained, at least in part, the reported intra and interfamilial phenotypic variability: the hormone resistance was usually present when the mutation was inherited from the mother, but absent when paternally inherited. It was also discovered that the loss of the normal

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parental-specific imprinting methylation pattern at *GNAS* differentially methylated regions (DMRs) led to a PHP phenotype typically characterized by PTH resistance without AHO features (PHP1B). Although most GNAS methylation defects were sporadic, in some familial cases they were produced by deletions of imprinting control elements (ICR) within *STX16* or *NESP55* upstream genes, and in a few cases also due to *GNAS* paternal uniparental isodisomy (UPD).[9,10] Additionally, independent studies highlighted the clinical and molecular overlap among PHP classic subtypes, comprising the presence of GNAS imprinting defects with no mutations in Gsα-coding exons in patients with a likely clinical diagnosis of PHP1A,[11] and revealed novel causative molecular defects and their prevalence.[12]

Despite the high detection rate of *GNAS* genetic and epigenetic defects, a subset of patients still lack(ed) a molecular diagnosis. The analysis of genes acting downstream Gsα in the cAMP-mediated signalling pathway, particularly *PRKAR1A* and *PDE4D* genes, enabled the identification of causative molecular alteration in a small (but increasing) subset of patients without *GNAS* defects. These results explained the phenotypic overlap between PHP and acrodysostosis, both phenotypically related skeletal disorders sometimes hard to distinguish only on the basis of clinical and radiological findings.[13-15] These findings also prompted the experts to develop a new classification for PHP and related disorders.[16] In an attempt to embrace and describe in a more effective and accurate way all the disorders known to be caused by abnormalities of their common signalling pathway, the term selected was ''inactivating PTH/PTHrP signalling disorder (iPPSD)''. The diagnosis is based only on clinical features (major and minor clinical criteria are proposed), and the integration of molecular findings is achieved through numbering each subtype. This new classification includes a variety of diseases under the same umbrella of a common pathogenic mechanism, provides with a clinical unifying diagnose, minimizes the clinical and molecular overlap between subgroups, and is open and capable to incorporate new incoming information.

Even if a validation (and if obtained, internationalization) of this iPPSD classification is needed, it is clear that a substantial progress has been achieved on the pathophysiology of PHP and related disorders throughout the world by physicians and research networks since 1942, but especially in the past 30 years. However, until very recently, caregivers and patients were still lacking guidelines for diagnosis and daily life care and treatment. With the aim of helping them from the clinical diagnosis, to the molecular confirmation of the genetic/epigenetic defect, up to the management of the most frequent manifestations of these rare diseases, an international consensus has just been stated.[17]

The approach comprised 2 years of work, 2 pre-consensus meetings, an expert consensus meeting, and a Delphi-like methodology, adjusted to rare diseases. An extensive literature search was employed to review more than 800 articles published between 1990 and 2016, and, after voting, 64 final recommendations with different levels of evidence and strength were approved: 14 on clinical diagnosis, 11 on molecular diagnosis and 39 on management and treatment. Globally, the maximum consensus and level of evidence, as considered by the experts, was reached

for 8 recommendations on clinical diagnosis, 5 on clinical management and 1 on molecular diagnosis.

The concept that the diagnosis should be based on clinical and biochemical characteristics concentrated one of the strongest consensus among experts. Among them, the major criteria should be PTH resistance, subcutaneous ossifications (can include deeper ossifications) and early-onset obesity associated with TSH resistance or AHO alone. The rest of the features (endocrine, neurological and others) would be supportive to the diagnosis. Similarly, the definition of PTH resistance was highly agreed as the association of hypocalcaemia, hyperphosphataemia and elevated serum levels of PTH in the absence of vitamin D deficiency, with normal magnesium levels and renal function. But even in the absence of overt hypocalcaemia, PTH resistance should be suspected when PTH is at – or above – the upper limit of normal, with normal calcifediol levels and hyperphosphataemia. Interestingly, the variability in the degree of PTH resistance and the evolving changes in serum calcium level, phosphorus and PTH in time, with the subsequent requirement of repeated testing before a definitive diagnosis is remarked. Genetic diagnosis should be considered in the presence of at least one major criteria, and severe symptomatic hypocalcemia should be managed according to the general guidelines stated for hypoparathyroidism.[17]

In summary, a historical view of these rare disorders from their first descriptions until nowadays, reinforces the importance of all the observations and contributions coming from clinicians, researchers and patients, as well as the acceleration of scientific progress in recent years. We hope that this wind of change, boosted by the spontaneous creation of active multidisciplinary international networks where patients and families have had a cohesive and decisive role, promotes further collaborations among groups and societies, and finally manages to significantly improve the quality of life of the affected individuals.

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