Inactivating PTH/PTHrP signaling disorders (iPPSDs): evaluation of the new classification in a multicenter large series of 544 molecularly characterized patients

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Abstract

Objective: Pseudohypoparathyroidism and related disorders belong to a group of heterogeneous rare diseases that share an impaired signaling downstream of G_{α} -protein-coupled receptors. Affected patients may present with various combination of symptoms including resistance to PTH and/or to other hormones, ectopic ossifications, brachydactyly type E, early onset obesity, short stature and cognitive difficulties. Several years ago we proposed a novel nomenclature under the term of inactivating PTH/PTHrP signaling disorders (iPPSD). It is now of utmost importance to validate these criteria and/or improve the basis of this new classification.

Design: Retrospective study of a large international series of 459 probands and 85 relatives molecularly characterized.

Methods: Information on major and minor criteria associated with iPPSD and genetic results were retrieved from patient files. We compared the presence of each criteria according to the iPPSD subtype, age and gender of the patients.

Results: More than 98% of the probands met the proposed criteria for iPPSD classification. Noteworthy, most patients (85%) presented a combination of symptoms rather than a single sign suggestive of iPPSD and the overlap among the different genetic forms of iPPSD was confirmed. The clinical and molecular characterization of relatives identified familial history as an additional important criterion predictive of the disease.

Conclusions: The phenotypic analysis of this large cohort confirmed the utility of the major and minor criteria and their combination to diagnose iPPSD. This report shows the importance of having simple and easily recognizable signs to diagnose with confidence these rare disorders and supports a better management of patients.

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Introduction

Pseudohypoparathyroidism (PHP) encompasses a spectrum of related, highly heterogeneous and frequently overlapping disorders deriving from molecular defects that impair the hormonal signaling via receptors coupled to the adenylyl cyclase by the α -subunit of the stimulatory G protein (G α) (1, 2, 3).

The term PHP includes several subtypes, including PHP type 1A (PHP1A, MIM#103580), PHP type 1B (PHP1B, MIM#603233) and PHP type 1C (PHP1C, MIM#612462), characterized by biochemical features of hypoparathyroidism due to peripheral resistance to the action of the parathyroid hormone (PTH) caused by genetic or epigenetic defects within or upstream the *GNAS* locus, that encodes for the G α (3). Frequently, patients also suffer from resistance to other hormones acting through G α -coupled receptors, such as the thyroid-stimulating hormone (TSH), gonadotropins, growth hormone-releasing hormone (GHRH) and calcitonin (3, 4). Additionally, individuals with PHP1A and PHP1C variably express early-onset obesity together with a series of physical features (pre- and/or post-natal growth retardation, dysmorphic facies, varying degrees of intellectual and/or cognitive impairment and development delay, brachydactyly and ectopic ossifications) termed Albright hereditary osteodystrophy (AHO) (5). The presence of AHO without PTH resistance is defined as pseudopseudohypoparathyroidism (PPHP, MIM#612463), while, in case of ectopic ossifications extending into deep muscles and connective tissues, as progressive osseous heteroplasia (POH; MIM#166350) (6). Acrodysostosis (ACRDYS, MIM#101800), that is associated with genetic defects in the *PRKAR1A* and *PDE4D* genes, also present signs similar to PHP such as brachydactyly, extensive facial dysmorphism, developmental delay and, frequently, PTH and TSH resistance (7, 8, 9). Molecular alterations in another PDE gene, the *PDE3A*, are finally associated with the autosomal dominant hypertension and brachydactyly type E syndrome (HTNB, MIM#112410), characterized by brachydactyly type E, severe salt-independent but age-dependent hypertension, increased fibroblast growth rate, altered baroreflex blood pressure regulation and juvenile death from a stroke when untreated (10).

Several research studies on the clinical and molecular background associated with different PHP subtypes demonstrated that the delay in obtaining a specific diagnosis often derives from the extremely variable presentation, the severity of PHP signs and symptoms

among patients, even in those carrying the same genetic alteration, as well as from the significant clinical and molecular overlap both among PHP subtypes and between PHP and the above mentioned related diseases (11, 12, 13, 14, 15). Moreover, a correct early diagnosis in infants and in individuals with atypical features is very rarely achieved because clinical symptoms may be isolated in infancy and considered as poorly specific; biochemical abnormalities typically worsen during childhood.

In 2016, the European Network for the study of PHP (EuroPHPnetwork) conducted an expert initiative to produce a new nomenclature and classification encompassing all disorders with impairments in PTH and/or PTHrP cAMP-mediated pathway in order to overcome the limits of the historical classification that disregarded related disorders. More importantly, the former classification did not consider molecular defects as distinctive criteria, thus failing to stratify many disorders including PHP and AHO. According to the novel proposal, the term inactivating PTH/PTHrP signaling disorder (iPPSD) was proposed instead of PHP, followed by a numbering for specific subtypes that allows the description of both clinical and molecular features (iPPSD1, loss-of-function variant in *PTHrP*; iPPSD2, loss-of-function alteration in *GNAS*; iPPSD3, methylation defects at one or more *GNAS* DMRs; iPPSD4, *PRKAR1A* pathogenic variant; iPPSD5, *PDE4D* pathogenic variant; iPPSD6, *PDE3A* pathogenic variant; iPPSDx, no molecular defect identified) (6). Such nomenclature will be used, together with the classical one when necessary, through the text.

The main advantages of the new suggested terminology can be summarized as (i) the definition of a common mechanism responsible for all diseases, (ii) the inclusion of non-genetically characterized patients into the classification, (iii) the avoidance of the ambiguous terms like 'pseudo' and (iv) the erasure of the clinical and molecular overlap between diseases.

Consequently, it is now of major importance to validate, and improve if necessary, the newly proposed classification. Hence, we propose a second position paper produced by the EuroPHPnetwork on the terminology and the classification of disorders characterized by the inactivation of the PTH/PTHrP signaling pathway. The aim of the present work was to evaluate a large, international case series of highly clinically and molecularly characterized patients by using the criteria recently proposed. In this large cohort of genetically confirmed patients, we investigated whether patients met the clinical major and minor criteria (16). In addition, we

considered still unexplored features to design additional objective criteria to guide an efficient distinction and stratification of iPPSD subtypes.

Patients and methods

This work was designed by clinicians and scientists from 3 tertiary centers (Italy, Spain and France) of the EuroPHPnet. Clinical and molecular data from 459 index patients (Supplementary Table 1, see section on [supplementary materials](#) given at the end of this article) and 85 relatives followed in their clinical centers and laboratories over the last decades were collected.

Inclusion criteria for the study were the availability of complete clinical data at the time of the clinical diagnosis of each patient and a confirmative molecular diagnosis of a (epi)genetic alteration at *GNAS*, *PRKARIA*, *PDE4D* or *PDE3A* loci.

Clinical features were divided into major (PTH resistance (rPTH), ectopic ossifications (EO) and brachydactyly type E (BR)) and minor criteria (TSH resistance, additional hormone resistances, motor and/or cognitive retardation or impairment, intrauterine growth restriction and/or post-natal growth retardation, obesity or overweight, and flat nasal bridge and/or maxillar hypoplasia and/or round face) according to the new proposal for diagnosis and classification (6). The minimum criteria for a clinical diagnosis of iPPSD were initially defined as at least one major criterion, either PTH resistance or ectopic ossifications or brachydactyly; in case of brachydactyly, 2 additional minor criteria were required as well (6).

The molecular workout to identify iPPSD/PHP-related alterations has been described previously (6, 16).

Only index cases were included in the analysis in order to prevent bias, while relatives were evaluated separately. All patients, legal guardians for minors and relatives involved in the study subscribed the informed consent for genetic studies and the treatment of personal and clinical data. All procedures were performed in compliance with relevant legislation and institutional guidelines and were approved by the IRCCS Fondazione Cà Granda Ospedale Maggiore Policlinico institutional committee (PHP2019, parere 15_2019bis), the comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé (CCTIRS, #13-028) under the promotion of the INSERM (Institut national de la santé et de la recherche médicale) (#DC-2013-1762), and the Basque Ethics Committee (IRB #PI2013214 and PI2017018).

Results and discussion

Validation of minimum criteria for iPPSD clinical diagnosis

The first and main aim of the present study was to test the detection rate achieved by re-evaluating our cohort of 459 PHP patients (205 males and 254 females) with a confirmatory molecular diagnosis following the proposals given by the EuroPHPnetwork in 2016. This meant to determine whether patients showed at least one major criterion between resistance to PTH (rPTH) and ectopic ossifications (EO) or brachydactyly (BR) associated with two minor criteria.

Out of the 459 patients, all but 8 patients (1.7%) met these minimum criteria, demonstrating a 98.3% detection rate. Thus, the proposed classification showed to work properly and allowed to identify almost all iPPSD patients at a first screening.

Of the 451 patients meeting the minimum criteria, 70 patients (15.5%) presented only 1 major criterion while 381 (84.5%) had either 1 major criterion associated with minor criteria or from 2 up to 3 major criteria with or without minor criteria (Fig. 1). As expected, although the age at diagnosis was not significantly different between these two subgroups, the mean age at diagnosis was slightly lower in

Figure 1

The clinical presentation in the 459 probands described in this paper: 70 patients (15.3%) presented only 1 major criterion while the great majority ($n = 381$, 83%) had either one major criterion associated with minor criteria or from two up to three major criteria with or without minor criteria. Only eight patients (1.7%) did not present any major criterion, thus not meeting the criteria to be clinically defined as iPPSD.

Figure 2

Clinical presentation according to age, independently of the iPPSD subtype. The figure shows the combination of major criteria with or without minor criteria for the whole cohort of probands and for each age group (infancy, from birth up to 2 years; early childhood, from 3 to 8 years; middle childhood, from 9 to 11 years; adolescence, from 12 up to 18 years; adulthood, over 18 years). Taken as a whole, the most frequent isolated major criteria was rPTH (12.4%), followed by BR associated with two minor criteria (2.6%) and EO (0.2%). During infancy, childhood, and adolescence/adulthood, the presence of complex phenotypes was found in 94%, 81–90%, and 76–78% of the patients, respectively.

investigated the correlation between the genetics and the patients' clinical presentation in our cohort (Table 3).

As previously observed in our study on the prevalence of PHP-associated molecular defects (17) we found that the 57 probands presenting with isolated PTH resistance were iPPSD3 due to *GNAS* methylation alterations. In particular, 70.2% had broad methylation defects and no known underlying primary genetic alteration, 26.3% had a deletion at the *STX16* gene and 3.5% presented broad methylation alterations secondary to UPD. As expected, the only patient showing ectopic ossifications with no additional signs carried a paternal *GNAS* point variant. Brachydactyly and 2 minor criteria were found almost in all types of iPPSDs, nearly half of them being iPPSD5, former acrodysostosis. We also confirmed that iPPSD4 and iPPSD5 diagnoses associate with a more complex and dysmorphic phenotype (31/37 patients with several major and minor criteria).

Several cases confirmed that there is a considerable overlap between what we have historically considered as different diseases, the most striking overlap being observed between the two most represented subtypes, that is iPPSD2 and 3 (historically PHP1A and 1B) (Fig. 3). As an example, patient IT208, who displayed brachydactyly plus 2 minor criteria, was diagnosed as iPPSD3 due to loss-of-imprinting

at all 4 *GNAS* DMRs. Several iPPSD3 patients with resistance to PTH presented additional major criteria and/or signs of AHO (mainly brachydactyly). In addition, patient IT108 diagnosed with iPPSD4 and a *PRKARIA* pathogenic variant did not develop PTH resistance, while 1 iPPSD2 case with *GNAS* alterations on the paternal allele (patient FR87) and 4 iPPSD5 patients (patients FR85, FR74, IT8p and FR62) showed resistance to the action of PTH. These findings further support the usefulness of the new classification and the impossibility for the former one to predict specific phenotypes, therefore preventing a proper follow-up.

Except for a higher prevalence of females in iPPSD5 (4 males vs 14 females), and increased age at diagnosis in iPPSD3, we found a similar sex ratio and similar age at diagnosis in the different iPPSDs. Only 1 patient with iPPSD3 caused by methylation defects at the *GNAS* locus was identified during infancy; this number increased proportionally with patients' age (48 patients diagnosed in childhood, 48 in adolescence and 94 in adulthood). This might be related to the lack of symptoms associated to PTH resistance and hypocalcemia (Supplementary Table 1); we know that, in patients with *GNAS* molecular defects, PTH resistance is absent at birth and develops overtime (17, 19, 20). In addition, hypocalcemia may be underdiagnosed for years, when developing slowly (16, 17, 19).

In 76 of the 224 iPPSD2 probands, we were able to define the parental inheritance of the genetic defect (63 on the maternal allele and 13 on the paternal one). The iPPSD3 group was mainly represented by patients with sporadic imprinting defects affecting all 4 *GNAS* DMRs. In iPPSD3 patients affected by the autosomal inherited *STX16* deletion, we were able to demonstrate the maternal origin in 8 out of 10 for whom information on parents, mother or father, were available. In addition, 4 women affected with iPPSD3 caused by *STX16* deletion and isolated loss of methylation at the *GNAS* A/B:TSS-DMR transmitted the deletion, the methylation defect and the iPPSD3 phenotype to their children. Out of 39 probands affected with non-imprinted genes like (*PRKARIA* in 19 iPPSD4, *PDE4D* in 18 iPPSD5 and *PDE3A* in 2 iPPSD6), we identified only 2 autosomal transmissions within the same family from mother to son and daughter (iPPSD4).

All the aforementioned data further support the absence of clear genotype–phenotype correlations. It reinforces the claim that the diagnosis of iPPSDs should be primarily clinical (16). Nevertheless, the same data strongly support the need to confirm the genetic diagnosis as the only way to identify a specific subtype, because of the dramatic clinical and molecular overlap among these heterogenous disorders (16).

Table 3 iPPSD index patients divided according to iPPSD subtype and in accordance with the presence of major/minor criteria used for diagnosis.

	iPPSD2			iPPSD3			iPPSD4	iPPSD5	iPPSD6
	Unknown inheritance	Mat allele	Pat allele	LoM <i>GNAS</i> A/B: TSS-DMR	LoI 4 DMRs	UPD			
Only minor	3	1	2		1			1	
BR <2 minor	2		2						
Only one major									
rPTH				15	40	2			
EO			1						
BR*	3		2		1			5	1
Plus major and/or minor									
rPTH+EO	1								
rPTH+BR	2				4				
EO+BR									
rPTH+EO+BR	1								
rPTH [§]	7	3		24	71	3	1	1	1
EO [§]	9		2						
BR [§]	4	1	2				1	8	
rPTH+EO [#]	13	3		1	1				
rPTH+BR [#]	52	22	1	4	27	1	16	3	
EO+BR [#]	5	1	3						
rPTH+EO+BR [#]	48	32			1		1		

*Plus 2 minor; [§]1 major plus ≥ 1 minor; [#] ≥ 1 minor.

BR, brachydactyly; EO, ectopic ossifications; LoI, loss of imprinting; LoM, loss of methylation; mat, maternal; pat, paternal; rPTH, resistance to PTH; UPD, uniparental disomy.

Minor criteria frequency and association with major criteria

Many symptoms of iPPSD are non-specific, as they are present in many endocrine and syndromic diseases, different from this group of disorders. Moreover, the number, the age of appearance and the severity of such features are extremely variable among patients, even

when bearing the same molecular alteration. Indeed, patients may develop a sequence of AHO features over time or clinical features may be faint and unnoticed at first examination. Therefore, we decided to determine, among the signs of AHO and other minor criteria, which ones could be considered as pathognomonic and more predictive of the diagnosis. We evaluated, in our cohort, the frequency, age of presentation and possible association of a series of symptoms with specific major criteria.

We counted how many times each single minor criterion was seen in patients, both alone and in combination with additional minor features. The most common symptoms identified were resistance to TSH, dysmorphic facies marked by a flat nasal bridge and/or a maxillary hypoplasia and/or a round face, obesity or overweight, intrauterine growth restriction and/or post-natal growth retardation, motor and/cognitive retardation or impairment and additional hormone resistances, for example to calcitonin, gonadotropins and/or GHRH in 282 (61.4%), 230 (50.1%), 199 (43.4%), 192 (41.8%), 148 (32.2%) and 90 (19.6%) iPPSD probands, respectively (Table 4 and Supplementary Table 1).

When we considered these clinical features as the unique minor criterion present in a given patient ($n = 91$), we found that resistance to TSH, intrauterine growth restriction and/or the post-natal growth retardation, obesity

Figure 3

Focuses on the clinical presentation of patients with the two numerically major iPPSD subtypes, that is iPPSD2&3 (historically PHP1A and 1B). The high degree of clinical overlap is shown, with several iPPSD3 probands showing brachydactyly, growth and/or weight disturbances, dysmorphic face or additional hormone resistances.

Table 4 Frequency of minor criteria in our cohort, both alone and in combination with additional signs.

	1 minor	≥2 minor	Total
rTSH	41	241	282
add HR	3	87	90
M/C imp	6	142	148
IUGR/PNGR	19	173	192
OB/OW	13	186	199
DF	9	221	230

add HR, additional hormone resistances; DF, facial dysmorphisms; IUGR/PNGR, intrauterine and/or postnatal growth retardation; M/C imp, motor and/or cognitive impairment or retardation; OB/OW, obesity or overweight; rTSH, resistance to TSH.

and overweight, and facial dysmorphism were the most frequent features in 41 (45.1%), 19 (20.9%), 13 (14.3%) and 9 (9.9%) patients, respectively (Table 4 and Supplementary Table 1). Noteworthy, intrauterine growth restriction and/or post-natal growth retardation were the unique minor criteria found in infants; mental and cognitive impairment was the most frequently reported in early childhood; resistance to TSH was the most frequent sign in the older groups; finally, the number of obese patients increased significantly from early childhood to adulthood (Fig. 4).

Overall and unfortunately, we were neither able to detect a specific minor sign nor a combination of signs allowing to establish a precise clinical diagnosis, that is the iPPSD subtype, or to predict the underlying genetic alteration. We conclude from our findings that these minor and major signs should be carefully searched during the first examination in order to promote an earlier detection of iPPSD in patients.

Relatives of index iPPSD patients

Great intrafamilial variability in the clinical presentation has been largely reported (16, 21). We took advantage of this rare, large and unique collection of 459 probands and 85 relatives to investigate this phenotypic diversity and the iPPSD detection in the patient's family circle.

The cohort of 85 relatives includes 36 mothers (M), 3 fathers (F), 12 descendants (D), that is 5 sons and 7 daughters, 30 siblings, that is 14 brothers and 16 sisters, 3 cousins (C) and one aunt (A) (Supplementary Table 2).

It is remarkable that one-third of the relatives ($n = 28$, 32.9%) were diagnosed through the family history and did not meet the minimum criteria to be classified as iPPSD. Among them, we identified 6 iPPSD3 and 22 iPPSD2 patients, including 6 with a paternal mutation at the *GNAS* gene. In particular, 18 subjects were apparently healthy with no major nor minor criteria, 5 patients

Figure 4

The frequency of minor criteria according to age groups. As shown, intrauterine growth restriction and/or post-natal growth retardation were the unique minor criteria present in infants, while in early childhood mental and cognitive impairment was most frequently reported; resistance to TSH was the most frequent sign in the older groups; finally, the number of obese patients increased significantly from early childhood to adulthood. Considering the whole cohort, resistance to TSH and growth alterations were mostly represented, followed by obesity/overweight and dysmorphic face.

had brachydactyly plus one minor criterion (4 growth retardation and 1 facial dysmorphism) and 5 patients showed minor criteria only (growth retardation, obesity, dysmorphic facies or resistance to TSH). The familial history, therefore, allowed a diagnosis of iPPSD before the occurrence of symptoms.

We then investigated the already known intrafamilial phenotypic variability of the disease and we observed that all index patients developed a more severe and complex clinical presentation compared to the parent from whom they inherited the molecular defect, either genetic or epigenetic, displaying a greater number of major and/or minor criteria (the overall presence of major and minor criteria in probands and relatives is summarized in Fig. 5). The same was true for the only aunt of the series. In a specular way, when we considered offsprings of affected patients, we found that, in half cases, the clinical phenotype was aggravated in the next generation. There were few exceptions, most of which is very young patients (1 year or less), in whom probably the phenotype had not yet become apparent (IT191d, FR32d2, FR64d, FR41d); in addition, IT84d is a healthy adult daughter of an iPPSD3 mother with rPTH and FR16d is a patient with two major and one minor criteria whose mother displayed three major and six minor criteria.

Figure 5

The overall presence of major and minor criteria in probands compared with the cohort of 85 relatives (36 mothers, 3 fathers, 5 sons, 7 daughters, 30 siblings, 3 cousins and one aunt). Independently of the intrafamilial phenotypic variability of the disease (see text), the figures show how each single major or minor criteria is more represented in index patients, who also develop a more severe and complex clinical presentation, compared to relatives. In addition, as shown, more than 30% of relatives did not show any major criteria.

All mutated siblings were affected and the clinical presentation was comparable to that of the index sibling. Patient IT217s, brother of a proband, was not considered in the analysis since no clinical data were available. Finally, the clinical features of the available couple of cousins were identical to the index case, similar to what we found in siblings (Supplementary Table 2).

Altogether, and in accordance to observations made in many other complex genetic disorders, our data suggest that, when present, the familial history of iPPSD should be also considered as a major criterion.

Concluding remarks

The investigation of a large, and unique cohort of 544 patients characterized by the inactivation of the PTH/PTHrP signaling pathway allowed us to propose this second position paper on the terminology and the classification of iPPSDs. The term ‘pseudohypoparathyroidism’ has been widely used to describe several highly related, metabolic disorders based on disputable clinical and biochemical grounds. Performing an early and correct diagnosis and a stratification into subtypes is challenging, due to the overlap between PHP and related disorders, and even among PHP subtypes. Additionally, the presentation and the severity are extremely variable among affected individuals, even among those carrying the same

molecular alteration. For this reason, in the recent past, a new nomenclature and classification has been proposed (6), and recommendations for the diagnosis and management of these patients have been published as a first international Consensus Statement (16).

The present study investigated the largest cohort of deeply clinically and molecularly characterized individuals affected by iPPSDs and allowed to evaluate the recently proposed criteria to define and classify these patients, although further prospective studies are needed to validate these observations. Overall, the phenotypic analysis of this large cohort confirmed the validity of the major and minor criteria and their combination to diagnose iPPSD, the new classification being able to correctly identify more than 98% of index patients at the time of their first clinical presentation. The further clinical characterization of iPPSD relatives importantly identified familial history as a new major criterion predictive of the disease.

In conclusion, our report shows the importance of having simple and easily recognizable signs to diagnose with confidence these rare disorders and support a better management of patients.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-20-0625>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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