From Pseudohyoparathyroidism to inactivating PTH/PTHrP Signalling Disorder (iPPSD): a novel classification proposed by the European EuroPHP-network

Susanne Thiele1,2,*, Giovanna Mantovani1,*, Anne Barlier3, Valentina Boldrin3, Paolo Bordogna4, Luisa De Sanctis4, Francesca M. Elli5, Kathleen Freson6, Intza Garín6, Virginie Grybek3,5, Patrick Hanna7,8, Benedetta Izzizi9, Olaf Hiort1, Beatriz Lecumberri10, Arrate Pereda7,9, Vrinda Saraff11, Caroline Silve9,10,11, Serap Turan12, Alessia Usardi16, Ralf Werner1, Guiomar Perez de Navarre2,5,*, Annès Linnart9,7,*

1University of Liége, Belgium. 2University of Milan, Milan, Italy. 3APHM, Laboratory of Molecular Biology, Marseille, France. 4University of Torino, Italy. 5University of Leuven, Belgium. 6UOS Arabia University Hospital, Vitoria-Gasteiz, Spain. 7APHP, Hôpital Bichat Paris Sud, Le Kremlin Bicêtre, France. 8INSERM U1169, France. 9La Paz University Hospital, Madrid, Spain. 10University of Basque Country, Leioa, Spain. 11Birmingham Children's Hospital, Birmingham, United Kingdom. 12APHP, Hôpital Cochin, Paris, France. 13Marmara University, Istanbul, Turkey.

Disorders caused by impairments in the parathyroid hormone (PTH) signalling pathway are historically classified under the term pseudohyoparathyroidism (PHP), that encompasses rare, related but highly heterogeneous diseases with demonstrated (epi)genetic causes. A defect in the response of the proximal renal tubule to PTH is the hallmark of all forms of PHP. AHO comprises heterogeneous clinical findings such as brachydactyly, rounded face, short stature, stocky build and subcutaneous ossifications likely mediated by the resistance to PTHrP at the growth plate during fetal and post-natal growth.

One objective of our network was to to review the limitations and challenges of the current nomenclature and recommend a novel classification for disorders impairing the PTH/PTHrP signalling pathway.

Main limits of the current classification
- Fails to stratify PHP and AHO
- Does not include acrodysostosis, POH and PTH1R-related chondrodysplasia
- Does not incorporate the genetics

Main demands for a new classification
- Simple and flexible
- Define the common mechanism of the disease
- Non ambiguous
- Based on the clinical Dg, but includes genetics

<table>
<thead>
<tr>
<th>PH1A</th>
<th>PPH</th>
<th>ADPH1B and sporPH1B</th>
<th>PH1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs</td>
<td>AHO</td>
<td>AHO</td>
<td>no</td>
</tr>
<tr>
<td>PTH-Resistance</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>In-vitro Ga3-activity</td>
<td>diminished</td>
<td>diminished</td>
<td>normal</td>
</tr>
</tbody>
</table>

Table 1: Current classification
ADPH1B: autosomal dominant form of PH1B
SporPH1B: sporadic form of PH1B

Major criteria
- PTH resistance
- Subcutaneous ossifications
- Brachydactyly type E*

Minor Criteria
- Thyroid Stimulating Hormone (TSH) resistance
- Other hormone resistances
- Motor and cognitive retardation or impairment
- IUGR and post-natal growth retardation
- Obesity, insulin resistance, hyperlipidaemia
- Flat nasal bridge and/or maxillar hypoplasia and/or round face

Minor criteria need to be combined with one or more major criteria to establish the diagnosis of iPPSD.

*Brachydactyly should be combined with at least one major or two minor criteria to trigger the diagnosis of iPPSD.