

VARIABILITY IN CLINICAL AND GENETIC SPECTRUM IN HYPOPHOSPHATASIA NATURAL HISTORY IN TWO PATIENTS

Martos-Moreno GÁ¹, Lerma S², García-Esparza E³, Argente J¹

¹Department of Endocrinology, Hospital Infantil Universitario Niño Jesús. Department of Pediatrics, Universidad Autónoma de Madrid. Instituto de Investigación La Princesa. CIBERobn, ISCIII. ²Laboratory for the analysis of movement. Orthopedics Department. ³Radiology Department. Hospital Infantil Universitario Niño Jesús. Madrid. Spain.

Introduction:

THE AUTHORS DECLARE NO CONFLICT OF INTERESTS

- Hypophosphatasia (HPP) is a congenital disorder of skeletal and tooth mineralization as a consequence of the deficiency in tissue non-specific alkaline phosphatase (TNSALP) caused by mutations in the *ALP/TNSALP* gene.
- Setting aside the HPP subtype with exclusive tooth impairment (*odonto-HPP*), the age at the onset of symptoms and their severity determine the classification of five clinical subtypes of HPP, with variable prognosis and major overlapping of phenotype.
- The pattern of inheritance of *ALP/TNSALP* mutations is complex, being autosomal recessive in the early and severe forms of HPP, whereas the mild / late forms of the disease are inherited in an autosomal dominant fashion.

Objective:

- To illustrate the mentioned phenotype variability in HPP, both in its clinical manifestations as in its pattern of genetic inheritance, by presenting the genetic and clinical features of two patients currently followed in our department.

Clinical case 1:

• Boy, with no familial background of bone or tooth disorders, born small for gestational age [38+5 weeks GA; 2250 g. (-2.22 SDS) and 45 cm (-2.60 SDS)]. Presented rachytic chest deformity starting at age 4 months, left coronal craniosynostosis and type 1 Arnold-Chiari malformation at age 10 months.

• Consulted at age 17 months due to lack of crawling and standing, with height 73.9 cm (-2.65 SDS), weight 8.4 kg (-2.43 SDS), head circumference 49 cm (+2 SDS for height), he showed (Figures 1 to 7):

- trunk hypotonia - dolichocephaly - delayed tooth eruption
- bell-shaped chest, rachitic rosary and pectus excavatum
- distal forearm metaphyseal widening
- metaphyseal flaring and areas of radiolucency at the X-rays

• He repeatedly displayed severely decreased ALP levels, with high plasma pyridoxal-5'-phosphate (PLP) and urine phosphoethanolamine (PEA), with no other analytical alteration (TABLE), caused by the mutations c.542C>T (p.S181L) and c.644T>C (p.I215T) in *ALPL* ("Infant HPP").

• At age 4.5 years, he presented more severe hypotonia (minimum muscle strength); failure to thrive (weight -3.00 SDS; height -3.80 SDS); chest deformity [involving functional impairment, FVC 54,2%], skeletal (craniolacunias) and tooth impairment (early tooth decay) (Figures 8 to 13). The described deformities resulted in severe impairment of walking, with maximum foot abduction and lack of knee flexing causing a typical waddling gait walking pattern. The patient is currently under therapy with recombinant human alkaline phosphatase in the setting of an ongoing Phase II clinical trial (ClinicalTrials.gov Identifier: NCT01176266).

Clinical case 2:

• Girl aged 9 months, born full term with suitable weight and length for gestational age, with no skeletal deformities but lacking tooth eruption. She consulted after the observation of repeatedly low ALP levels. Despite the normal results in the radiological skeletal survey and the lack of associated analytical alterations, she showed increased PLP plasma levels. This was due to a heterozygous deletion c.217-219delCTC (p.L73del) in *ALPL*, inherited from her mother.

• The patient's mother displayed (at an adult age) typical signs of adult HPP (i.e. frequent cariation, leg pain at the end of the day limiting her activity), interestingly with ALP and PLP in the lower normal range.

Conclusions:

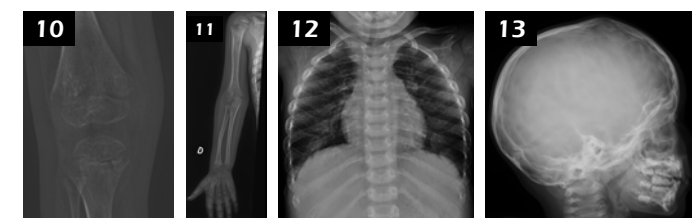
- HPP shows a wide genetic spectrum, without a strict clinical correlate and with phenotypic features overlapping between the different forms of the disease.
- High plasma PLP with low ALP levels is a good analytical marker that allows for the suspicion of HPP in children.

	Case 1	Case 2	Reference values
Serum alkaline phosphatase	23 / 31 U/L	75 / 72 / 85 U/L	(122-290)
Plasma pyridoxal 5' phosphate	>300 µg/l	>300 µg/l	(4-18)
Phosphoethanolamine (urine)	1395 µmol/g creatinine	—	(1-362)
Serum total calcium	9.6 mg/dl	9.8 mg/dl	(8.8-10.8)
Serum ionic calcium	1.2 mmol/l	1.3 mmol/l	(1.1-1.4)
Serum magnesium	2.3 mg/dl	2.1 mg/dl	(1.5-2.3)
Serum phosphorus	6.5 mg/dl	6.5 mg/dl	(4.5-7.5)
25-hydroxy-vitamin D	32.3 ng/ml	26.7 ng/ml	(20-100)
1-25 dihydroxy vitamin D	69.5 pg/ml	59.8 pg/ml	(18-78)
Intact PTH	22.3 pg/ml	41.3 pg/ml	(11-47)

Abbreviation: PTH: Parathyroid hormone



Figures 1 to 7: Clinical and radiological phenotype of patient 1 at his first visit [age 17 months]. It is of note the cranial asymmetry as a consequence of his craniosynostosis, the chest deformity and distal metaphyseal widening of the forearms. In the X-ray films the typical radiological findings of Infant and childhood HPP can be observed: metaphyseal flaring and areas of radiolucency, next to the sparse radiological density of bones and the deformity of the rib cage.



Figures 8 to 13: Clinical and radiological phenotype of patient 1 at age 4.5 years. It is remarkable the hypotonic appearance, the intensification of chest deformity and the early deciduous tooth decay. X-ray films confirm the sparse radiological density of bones and show the development of craniolacunias.