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SPECIAL ARTICLE

Hypophosphatasia: Clinical manifestations, diagnostic recommendations and therapeutic options☆

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Abstract Hypophosphatasia is a very rare bone metabolism disorder caused by a deficiency in alkaline phosphatase activity, due to mutations in the *ALPL* gene. Its clinical hallmark is the impairment of skeletal and tooth mineralization, although extra-skeletal manifestations are frequent. Its phenotypic spectrum is widely variable from a subtype with exclusive odontological impairment (odontohypophosphatasia) to five subtypes with systemic involvement, classified according to the age at the onset of the first symptoms (four of them in the paediatric age range: perinatal lethal, perinatal benign, infant and childhood hypophosphatasia). Those subtypes of hypophosphatasia with an earliest onset usually involve a worse prognosis, due to the risk of developing potentially lethal complications, such as seizures or severe respiratory insufficiency, secondary to rib cage malformations. Due to the extremely low prevalence of the severe forms of hypophosphatasia, its clinical variability and overlapping phenotypic features with several more prevalent conditions, the diagnosis of hypophosphatasia in the clinical setting is challenging. However, its potential lethality and impact on the patient's quality of life, along with the recent availability of an enzyme replacement therapy, increases the relevance of the early and accurate identification of patients affected with hypophosphatasia. On the basis of published evidence and clinical experience, this article suggests an algorithm with practical recommendations for the differential diagnosis of childhood hypophosphatasia, as well as an updated review of current therapeutic options.

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Hipofosfatasia: manifestaciones clínicas, recomendaciones diagnósticas y opciones terapéuticas

Resumen La hipofosfatasia es una enfermedad ultra-rara del metabolismo mineral óseo causada por un déficit de actividad de la fosfatasa alcalina, debido a la existencia de mutaciones en el gen *ALPL*. Clínicamente, se caracteriza por el desarrollo de hipomineralización esquelética y dental, junto con la frecuente aparición de manifestaciones extraesqueléticas. Su espectro fenotípico es muy variable y engloba una forma de afectación exclusivamente odontológica (odontohipofosfatasia) y 5 subtipos de afectación sistémica diferenciados según el momento de inicio de los síntomas (4 de los cuales se desarrollan en la edad pediátrica: formas perinatal letal, perinatal benigna, del lactante e infanto-juvenil). Las formas de inicio más precoz presentan, generalmente, peor pronóstico, debido a la posibilidad de desarrollar complicaciones potencialmente letales, como la dificultad respiratoria grave por malformaciones torácicas o la presencia de convulsiones. Debido a la baja prevalencia de las formas graves de la enfermedad, y a su variabilidad y solapamiento fenotípico con otras patologías más prevalentes, el diagnóstico de la hipofosfastasia en la práctica clínica constituye un reto. No obstante, su potencial gravedad e impacto sobre la calidad de vida de los pacientes, así como la reciente disponibilidad de un tratamiento de reemplazo enzimático específico, confieren particular relevancia a la correcta identificación de los pacientes afectos de hipofosfatasia. A partir de la evidencia publicada y la experiencia clínica, en el presente artículo se propone un algoritmo con recomendaciones prácticas para el diagnóstico diferencial de la hipofosfatasia en niños, así como una revisión actualizada de las opciones de tratamiento existentes.

Hypophosphatasia: the clinical entity

Hypophosphatasia (HPP) is an extremely rare disease of calcium and phosphate metabolism with systemic involvement and a progressive course, characterized by defective bone mineralization due to reduced activity of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP).[1,2] Alkaline phosphatase (ALP) is a key enzyme in bone and tooth mineralization of which there are at least 4 isoenzymes: TNSALP (which accounts for 95% of the total serum ALP activity) and 3 tissue-specific isoenzymes (intestinal, placental and germ cell).[1,2] The TNSALP isoenzyme is encoded by the *ALPL* gene (1p36.12; OMIM 171760), which is mainly expressed in liver, bone, kidney, muscle and sensory areas of the cerebral cortex.[3] The presence of variants in *ALPL* associated with changes in TNSALP function determines the development of HPP, and more than 330 mutations have been described to date.[4]

The main substrates of TNSALP are inorganic pyrophosphate (PPi), pyridoxal 5′-phosphate (PLP) and phosphoethanolamine (PEA).[3] In patients with HPP, low TNSALP activity leads to accumulation of these substrates and the manifestations associated with the disease. The high concentration of PPi in the extracellular osseous matrix prevents the nucleation of calcium and phosphate crystals, interfering with the growth of hydroxyapatite crystals and leading to skeletal abnormalities.[3] On the other hand, the dephosphorylation of PLP (an active metabolite of vitamin B6 or pyridoxine) to pyridoxal (PL) by TNSALP is necessary for pyridoxine to cross the cell membrane or the blood-brain barrier. Pyridoxal 5′-phosphate is an essential cofactor of inhibitory neurotransmitters such as gamma-aminobutyric acid. Symptomatic neonatal and infantile forms of HPP characteristically manifest with seizures secondary to a central deficiency of vitamin B6, despite the accumulation of PLP in plasma.[1–3] In addition, the frequent presence of inflammatory damage in the joints in patients with HPP suggests that TNSALP plays a role in inflammatory processes activated by the deposition of calcium pyrophosphate dihydrate crystals.

Historically, hypophosphatasia has been classified into a form with exclusive involvement of tooth (odontohypophosphatasia) and 5 subtypes with systemic involvement classified according to age at onset (4 paediatric forms and 1 adult form) (Tables 1–3). At present, it is also important to differentiate between mild and severe forms, at least in the infantile and childhood subtypes.[1] Furthermore, there have been descriptions in the literature of another disease with manifestations that are similar to those of HPP but with a normal or even mildly elevated serum TNSALP activity (pseudohypophosphatasia),[1] although in these cases, activity in the normal range might be due to intercurrent conditions.[1]

Generally, forms with earlier onset have a poorer prognosis[1,2,5] due to the potentially fatal complications of skeletal abnormalities (severe respiratory difficulties due to chest deformities) or extraskeletal manifestations (presence of seizures).[6]

The prevalence of severe forms of HPP is estimated at 1 case per 300,000 births in Europe.[5] It varies between populations, with severe forms being most frequent in Canadian Mennonites (1:2500)[2] and perinatal lethal forms in Japan.[7] The prevalence of mild forms with a dominant pattern of