SPECIAL ARTICLE

Hypophosphatasia: Clinical manifestations, diagnostic recommendations and therapeutic options

Gabriel Ángel Martos-Morenoa,*, Joan Calzada b, María L. Couce c, Jesús Argente a,d

a Servicio de Endocrinología, Hospital Infantil Universitario Niño Jesús, Instituto de Investigación Sanitaria La Princesa, Departamento de Pediatría, Universidad Autónoma de Madrid, CIBERobin, Instituto de Salud Carlos III, Madrid, Spain
b Respuesta inflamatoria sistémica en pediatría, Institut de Recerca Sant Joan de Déu, Sección de Reumatología Pediátrica, Servicio de Pediatría, Hospital Sant Joan de Déu, Esplugues de Llobregat, Barcelona, Spain
c Unidad de Diagnóstico y Tratamiento de Enfermedades Metabólicas Congénitas, Servicio de Neonatología, Complejo Hospitalario Universitario de Santiago, CIBERER, IDIS, Santiago de Compostela, La Coruña, Spain
d Instituto de Alimentación IMDEA, CEI UAM-CSIC, Madrid, Spain

Received 20 April 2017; accepted 12 June 2017
Available online 5 May 2018

KEYWORDS
Hypophosphatasia; Hypo-mineralization; Alkaline phosphatase; Asfotase alfa

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.

© 2017 Asociación Española de Pediatría. Published by Elsevier España, S.L.U. All rights reserved.

* Please cite this article as: Martos-Moreno GÁ, Calzada J, Couce ML, Argente J. Hipofosfatasia: manifestaciones clínicas, recomendaciones diagnósticas y opciones terapéuticas. An Pediatr (Barc). 2018;88:356.e1–356.e11.
* Corresponding author.
E-mail address: gabrielangelmartos@yahoo.es (G.Á. Martos-Moreno).

2341-2879/© 2017 Asociación Española de Pediatría. Published by Elsevier España, S.L.U. All rights reserved.
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 extrasesqueléticas. 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 hipofosfatasia 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.

© 2017 Asociación Española de Pediatría. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.
Hypophosphatasia: Diagnosis and treatment

Table 1  Clinical features of perinatal forms of hypophosphatasia.

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Age at onset</th>
<th>Main clinical manifestations</th>
<th>Diagnostic tests</th>
<th>Natural history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal lethal form (AR inheritance)</td>
<td>Perinatal period (sonographic signs detectable prenatally)</td>
<td>Skeletal malformation(^2,20) Severe hypomineralization Long bone shortening and bowing Absence of ossification of cranial dome save for calcification of central area (caput membranaceum) Osteochondral spurs in ulna and fibula (characteristic) Fractures and bone fragility Neurologic abnormalities Vitamin B6-dependent seizures Hypersensitivity to stimuli (irritability) Intracranial haemorrhage (possible) Other changes(^21) Severe pulmonary hypoplasia (secondary to chest deformity) Clinically relevant apnoea Idiopathic fever Myelophthisic anaemia Hypercalcemia Hypomagnesaemia</td>
<td>Imaging tests Radiograph: characteristic associated skeletal abnormalities Ultrasound: characteristic associated malformations Laboratory tests Total TNSALP activity (cord blood sample): low Genetic testing/prenatal diagnosis (cord blood or chorionic villus sampling) Pathogenic mutations in ALPL gene</td>
<td>Most severe form, minimal long-term survival Frequent intrauterine fetal death or neonatal death in the first days or weeks post birth</td>
</tr>
<tr>
<td>Benign perinatal form (AR/AD inheritance)</td>
<td>Perinatal period (sonographic signs detectable prenatally)</td>
<td>Skeletal abnormalities Hypomineralization Long bone shortening and bowing</td>
<td>Imaging tests Radiograph: characteristic associated skeletal abnormalities Ultrasound: characteristic associated malformations Laboratory tests Total TNSALP activity (cord blood sample): low Genetic testing/prenatal diagnosis (cord blood or chorionic villus sampling) Pathogenic mutations in ALPL gene</td>
<td>Spontaneous improvement of skeletal abnormalities after birth with a favourable prognosis (long-term outcomes in the natural history of this form are unknown)</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; ALPL, tissue-nonspecific alkaline phosphatase gene; TNSALP, tissue non-specific alkaline phosphatase; AR, autosomal recessive.

Inheritance is estimated at 1 case in 6370 births in Europe.\(^8\) In contrast, the prevalence of hypophosphatasemia (low serum ALP activity) is much higher, as this state may be due to multiple causes in the absence of HPP (Table 4). The diagnosis of HPP in clinical practice poses challenges due to the low prevalence of the disease and the considerable phenotypic overlap with other diseases that are more common. Furthermore, the little importance that is normally given to low serum ALP activity (compared to the usual assessment that follows detection of hyperphosphatasemia) is a limiting factor in the diagnosis of HPP. Yet, diagnosis is particularly important given the potential severity of the disease, the considerable impact it has in the quality of life of many of those affected, or the iatrogenic problems that could result from misdiagnosis. Furthermore, a targeted enzyme replacement therapy for HPP has recently become available,\(^9,10\) so correct diagnosis is now even more crucial to allow early and appropriate treatment.

The main aim of this article is to provide general recommendations to facilitate the identification of paediatric patients with HPP. We recommend that those seeking detailed information on the genetic basis, pathophysiology and clinical manifestations of the disease consult recently published literature reviews on the subject.\(^1,2,6,10\)

Diagnosis of hypophosphatasia

Fig. 1 shows an algorithm for the diagnosis of HPP in paediatric patients based on current evidence and expert recommendations derived from clinical experience. It aims to provide a logical sequence for diagnosis of potential cases of symptomatic HPP, although there are forms of the dis-
ease with minimal to non-existent clinical manifestations in childhood and adolescence. In such cases, persistence of low serum TNSALP activity, even in the absence of skeletal manifestations, may suggest the presence of a mild form of HPP (whose severity may increase in adulthood). A diagnosis of HPP should be considered mainly in patients presenting with certain musculoskeletal or dental signs and symptoms (although in severe perinatal and infantile forms, respiratory and neurologic symptoms are strongly suggestive of HPP). Tables 1–3 list the most frequent clinical features of the paediatric forms of HPP.

In the lethal perinatal form, the radiologic features are highly indicative of HPP: absence of mineralization in some bones (for which the main differential diagnosis would be osteogenesis imperfecta), caput membranaceum and osteochondral spurs in forearms and legs (a pathognomonic finding) (Fig. 2). 1 While hypocalcaemia and hypophosphataemia are associated with different types of rickets, HPP may manifest with hypercalcemia and hyperphosphataemia (prevalence up to 50%), and low serum levels of calcium and phosphate are rare in this disease. 11 The cause of hypercalcemia is unknown, although it could be due to impaired calcium uptake in bone. Hyperphosphataemia results from increased tubular reabsorption of inorganic phosphate. 1

In the benign perinatal form, prenatal ultrasound examination reveals signs of reduced mineralization in the long bones, but patients start improving spontaneously in the third trimester and may have a normal development.
Table 3 Clinical features of childhood hypophosphatasia.

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Age at onset</th>
<th>Main clinical features</th>
<th>Diagnostic tests</th>
<th>Natural history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood form (AR/AD inheritance)</td>
<td>After 6 months post birth</td>
<td>Skeletal abnormalities(^{12,22}) Hypophosphominalization/rachitic deformities Weight faltering, short stature Recurrent fractures Shortening and bowing of long bones Rachitic rosary/chest deformity Metaphyseal flaring Scoliosis Reduced bone mineral density Craniofacial abnormalities(^{22}) Craniosynostosis Raised intracranial pressure Proptosis Dolichocephaly Psychomotor changes(^{23}) Delay in motor development milestones (independent walking) Waddling gait Dental abnormalities(^{5,11,16}) Delayed tooth eruption and premature loss of deciduous teeth without root resorption (characteristic) Enlarged pulp chambers Loss of alveolar bone Frequent and severe caries Other abnormalities(^{23}) Chronic bone and joint pain Hypotonia Excessive fatigue Loss of appetite Gastrointestinal disorders</td>
<td>Comprehensive anamnness. Imaging tests Radiograph: typical skeletal abnormalities Bone densitometry: low bone density Laboratory tests Total TNSALP activity: low Elevation of TNSALP substrates: PLP in plasma, PEA in plasma and urine Genetic testing (blood sample): pathogenic mutations in (ALPL) gene</td>
<td>Form with a variable prognosis depending on the severity of clinical manifestations. In some cases, there is spontaneous remission of skeletal abnormalities after puberty, although they may recur in adulthood(^{5,11})</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; ALPL, tissue-nonspecific alkaline phosphatase gene; TNSALP, tissue-specific ALP; AR, autosomal recessive; PEA, phosphoethanolamine; PLP, pyridoxal 5'-phosphate.

The most characteristic findings of infantile HPP are bone and muscle pain (with or without fractures), skeletal deformities similar to those observed in patients with rickets, impaired weight gain hypotonia/muscle weakness and delays in achievement of psychomotor development milestones.\(^6\) The most frequent skeletal abnormalities are rachitic chest deformity, bowing of the long bones, genu varum (after achieving independent standing), bone fractures and craniosynostosis. This corresponds to detection of metaphyseal widening, fraying and radiolucencies in the long bones in imaging tests\(^{5,11,12}\) (Fig. 2b).

There is often a significant overlap between the presentation of the most severe forms of infantile HPP and the presentation of the perinatal lethal form. Respiratory difficulties resulting from chest deformities predispose infants to pneumonia and respiratory failure and are the leading cause of death in these patients.\(^1,2\) Craniosynostosis may cause raised intracranial pressure, which may be associated with Arnold Chiari type I malformation, hydrocephalus and hydroxyngomyelia, among other central nervous system abnormalities.\(^1,2,5,6\) Raised intracranial pressure and calcification of the basal ganglia may play a role, along with changes in PLP metabolism, in the development of the seizures characteristic of perinatal and infantile HPP, which are associated with a poor prognosis and a high mortality.\(^5,11\)

Low parathyroid hormone levels are common in infantile HPP. The reduced secretion of this hormone could be due to hypercalcemia and in turn lead to the development of hyperphosphataemia. In addition, hypercalcemia and hypercalciuria could lead to development of nephrocalcinosis, so performance of kidney ultrasound examinations at regular intervals is recommended as part of the follow-up.\(^14\)

Despite the poor prognosis of this form of HPP, some patients experience a spontaneous improvement in bone mineralization with the corresponding clinical improvement. Patients with infantile HPP may develop neurologic complications associated with craniosynostosis, have a short stature and loose teeth prematurely, but have a more favourable prognosis compared to patients with perinatal HPP.\(^5,11\)

Childhood HPP follows in the continuum of disease after infantile HPP, with onset usually occurring after age 1 year.\(^1,2\) The main radiologic feature is the presence of characteristic projections of non-ossified tissue in the epiphyseal plates ("tongues" of radiolucency), which differentiate HPP from
Figure 1  Algorithm for diagnosis of hypophosphatasia in paediatric patients. ALPL tissue nonspecific alkaline phosphatase gene; TNSALP, tissue non-specific alkaline phosphatase; HPP, hypophosphatasia; PEA, phosphoethanolamine; PLP, pyridoxal 5’-phosphate.

*In ≥ 2 measurements, with no history of normal ALP activity levels and in the absence of acute disease. **PEA has a low specificity and is not always elevated in HPP. Patients with HPP often have a total TNSALP activity level at the limit of detection, while in less severe forms of disease the level may be at the lower limit of normal or mildly decreased. A decrease in TNSALP activity results in accumulation of TNSALP substrates. ***A diagnosis of HPP should not be ruled out in patients in whom other causes that may account for the clinical manifestations could not be identified, regardless of the levels of TNSALP substrates.

The first step in diagnosis when HPP is suspected is measurement of the total TNSALP activity. Reference values in children vary based on age, sex and the assay used (Table 5). It is important to take into account that mild forms of HPP may manifest with levels of TNSALP activity that are only slightly reduced or even at the lower limit of normal. Furthermore, there are multiple conditions that may manifest with a low total serum TNSALP activity (Table 4), so it is also important to assess the potential elevation of certain TNSALP substrates. In children with HPP, the degree of PLP accumulation in plasma is associated with the severity of disease, and this is the most sensitive and specific marker for diagnosis of HPP. Based on the current international literature, the positive and negative predictive values of PLP for

various forms of rickets and metaphyseal dysplasia. Presentation with mild hypercalcemia and hypercalciumia is less frequent in the childhood form, and serum levels of parathyroid hormone and vitamin D are usually normal (or slightly reduced in patients with renal compromise).

Clinicians should take into account the risk of craniosynostosis in every paediatric form of HPP, and patients should undergo neurologic evaluations at regular intervals, including ophthalmoscopy, until they reach adolescence. It is also important to monitor patients that only have dental manifestations, as they may eventually develop other abnormalities. There is evidence that the severity of HPP is associated with the number of teeth lost and inversely correlated to the age at loss of the first tooth.
Hypophosphatasia: Diagnosis and treatment

Figure 2  Characteristic findings of imaging tests in cases of perinatal lethal hypophosphatasia (a) and infantile hypophosphatasia (b). (a) Ultrasound at 18 weeks’ gestation: bone spurs in right knee and right elbow (3D). (b) Radiologic evaluation in patient aged 17 months: marked changes in long bone metaphyses (proximal metaphyses of both humeri, distal metaphyses of both radii and ulnae, and proximal metaphyses of both femora, tibiae and fibulae), with metaphyseal flaring, reduced bone density, thickened trabeculae and radiolucent projections that extend from physis to metaphysis. Linear periosteal reaction in the left radius. Images reproduced with the authorization of Zankl A, Mornet E, Wong S. Specific ultrasonography features of perinatal lethal hypophosphatasia. Am J Med Gen Part A. 2008;146A:1200–1204, and Caballero Mora FJ, Martos Moreno GA, Garcia Espanza E, Argente J. Hipofosfatasi infantil. An Pediatr. 2012;76:368–369.

diagnosis in children are very high, although absence of elevation of serum levels of PLP or other substrates of TNSALP (PEA, PPI) is not enough to rule out HPP. Measurement of bone mineral density by dual-energy X-ray absorptiometry may reveal low bone density, although this feature is not required for diagnosis.

In patients presenting with clinical manifestations suggestive of HPP and low levels of total serum TNSALP activity (in the absence of another identifiable cause), with or without elevation of TNSALP substrates, other diseases that are more prevalent and whose manifestations overlap with those of HPP need to be ruled out before making the diagnosis (Table 6).

Detection of mutations in the ALPL gene through molecular analysis can help establish the diagnosis in uncertain cases or serve as confirmation of HPP. However, some
Table 4 Situations that may be associated with low alkaline phosphatase activity.

<table>
<thead>
<tr>
<th>Pathologies</th>
<th>Low alkaline phosphatase activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pernicious or severe anaemia</td>
<td>Situations related to clinical management or laboratory testing</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Vitamin C deficiency</td>
<td>Immobilization</td>
</tr>
<tr>
<td>Zinc or magnesium deficiency</td>
<td>Cardiac bypass surgery</td>
</tr>
<tr>
<td>Cleidocranial dysplasia</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Starvation</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Inadequate sample</td>
</tr>
<tr>
<td>Vitamin D toxicity</td>
<td>Collection technique</td>
</tr>
<tr>
<td>Exposure to radioactive heavy metals</td>
<td>Use of inappropriate reference ranges</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Treatment with clofibrate</td>
</tr>
<tr>
<td>Osteogenesis imperfecta</td>
<td>Blood or plasma</td>
</tr>
<tr>
<td>Milk-alkali syndrome</td>
<td>Transfusion</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td></td>
</tr>
</tbody>
</table>

EDTA, ethylenediaminetetraacetic acid.

authors consider that in cases with a presentation that is clearly indicative of HPP (clinical manifestations + radiologic features + biochemical profile), mutation analysis is not required for diagnosis.1

Mutation analysis of samples obtained by amniocentesis may be performed in pregnant women in whom fetal abnormalities compatible with HPP have been detected or who have previous children with the disease, although its use is controversial, as it is not possible to differentiate reliably between the lethal and benign perinatal forms until late in the pregnancy.1,2

Management of hypophosphatasia

The management of HPP should be multidisciplinary and tailored to each patient according to the presentation and severity of the disease. Patients should be followed up in medical centres with specialists in metabolic bone diseases. At present, while there is no cure for HPP, patients can receive enzyme replacement therapy.9,17

Due to the symptoms it produces and its poor prognosis, severe perinatal HPP is managed differently, so we have devoted a separate section to this particular form (the remaining sections refer to the management of all paediatric forms of HPP).

Severe perinatal hypophosphatasia

First of all, if hypophosphatasia is suspected before birth, it is recommended to transfer the mother to a hospital with a level III B–C neonatal intensive care unit.

Respiratory support is key in severe perinatal HPP due to the increased risk of developing pulmonary hypoplasia with respiratory failure, which usually requires intubation and mechanical ventilation after birth. The newborn may need
Table 6 Differential diagnosis of hypophosphatasia in the paediatric age group.

<table>
<thead>
<tr>
<th>Category</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal HPP</td>
<td>Osteogenesis imperfecta (severe forms, such as type i)</td>
</tr>
<tr>
<td></td>
<td>Congenital dwarfism</td>
</tr>
<tr>
<td></td>
<td>Camptomelic dysplasia</td>
</tr>
<tr>
<td></td>
<td>Chondrodysplasias with abnormal bone mineralization</td>
</tr>
<tr>
<td></td>
<td>Severe hyperparathyroidism</td>
</tr>
<tr>
<td></td>
<td>Inborn errors of energy metabolism</td>
</tr>
<tr>
<td></td>
<td>Organic aciduria</td>
</tr>
<tr>
<td></td>
<td>Primary and secondary rickets</td>
</tr>
<tr>
<td>Infantile and</td>
<td>Osteogenesis imperfecta</td>
</tr>
<tr>
<td>childhood HPP</td>
<td>Achondrodysplasia</td>
</tr>
<tr>
<td></td>
<td>Periodontitis</td>
</tr>
<tr>
<td></td>
<td>Cleidocranial dysplasia</td>
</tr>
<tr>
<td></td>
<td>Cole-Carpenter syndrome</td>
</tr>
<tr>
<td></td>
<td>Idiopathic juvenile osteoporosis</td>
</tr>
<tr>
<td></td>
<td>Renal osteodystrophy</td>
</tr>
<tr>
<td></td>
<td>Chronic nonbacterial osteomyelitis</td>
</tr>
<tr>
<td></td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td></td>
<td>Idiopathic hypercalcemia and other causes of nephrocalcinosis</td>
</tr>
<tr>
<td></td>
<td>Neglect and non-accidental injury</td>
</tr>
</tbody>
</table>

High-frequency ventilation, nitric oxide, pharmacological treatment (sildenafil, milrinone) and even extracorporeal life support.

Serum levels of TNSALP activity calcium, phosphate and markers of renal function must be closely monitored, performing measurements every 48–72 h in the first week of life and weekly thereafter as required by the patient’s condition. A cranial ultrasound examination should be performed in the first 48 h post birth, and possibly repeated at a later time based on the condition of the patient.

If prolonged respiratory support is required after the initial acute phase, the patient should be assessed for the presence of tracheobronchomalacia, which requires ventilation with high-expiratory pressures.

Brain function should be monitored by amplitude-integrated electroencephalography to detect convulsive seizures that may not be apparent based on clinical manifestations, whose presence, if detected, should be confirmed by means of conventional electroencephalography. Seizures are treated with intravenous pyridoxine (loading dose of de 100 mg followed by 15–30 mg/kg/day administered in 3 doses a day).

Dietary interventions and supportive care (patients of all ages)

In case of hypercalcemia, dietary calcium intake should be restricted and care taken to ensure adequate hydration. Treatment with glucocorticoids or diuretic agents may be considered in severe cases, although loop diuretics should be used with caution, as they may exacerbate hypercalcuiara. If the serum levels of calcium and phosphate are normal or only mildly elevated, the patient can follow a diet with a normal calcium intake, as calcium supplementation may aggravate hypercalcemia and hypercalcuiara. Vitamin D3 supplementation should be avoided unless the patient has a deficiency (although it is not necessary to reduce exposure to sunlight), as calcium and/or vitamin D3 supplementation in these cases has been associated with hypercalcemia, hyperphosphataemia and hypercalcuiara.

Dental health should be monitored through regular checkups, promoting adequate oral hygiene.

The degree of functional impairment caused by HPP mainly depends on the musculoskeletal, neurologic and pulmonary abnormalities associated with the disease, so it is important that rehabilitation specialists and physical therapists are involved in the management of these patients.

Medical treatment

There is no standard medical treatment for HPP, and different approaches have been used with heterogeneous results.

Calcitonin has been used with the aim of decreasing bone resorption, with poor results. Bisphosphonates can be detrimental in HPP. They are PPI analogues, so they contribute to the inhibition of hydroxyapatite crystal growth, and they can bind zinc and magnesium cations, thereby compromising any residual TNSALP activity.

Nonsteroidal anti-inflammatories may be useful for pain relief, especially in patients with bone marrow oedema, and for treatment of extra-articular calcifications.

Enzyme replacement therapy was first tested using intravenous infusions of plasma enriched with TNSALP from patients with Paget bone disease or purified from human placenta. Although there was transient improvement in serum markers, there was no improvement in symptoms or radiologic features, and the results could not be replicated. An isolated increase in the serum level of TNSALP is not sufficient for treatment to be effective, as levels of the enzyme need to be restored within bone tissue. Other approaches for replacement that have been investigated are bone marrow transplantation and transplantation of allogeneic mesenchymal cells committed to the osteoblast phenotype. Although they achieve a degree of clinical improvement, it is important to consider the subsequent need for immunosuppressive therapy and the associated morbidity. Gene therapy with transfection of the ALPL gene through a lentiviral vector has also been tried in ALPL knockout mice.

Since 2015, asfotase alfa has been authorized by the European Medicine Agency (EMA) for treatment of severe forms of perinatal, infantile and childhood HPP. It is a recombinant fusion protein comprising the catalytic domain of the TNSALP linked to the constant region of the IgG1 domain and a terminal decaaspartate motif for bone targeting. The first results of a clinical trial of asfotase alfa for treatment of severe perinatal or infantile HPP were published in 2012. There was significant improvement in skeletal quality, respiratory function, motor and cognitive development and myopathy, and a rapid decline in serum levels of PLP and PPI, findings that were corroborated in a later trial with a longer duration of treatment.

Asfotase alfa has been found to increase survival in patients with HPP (from 27% to 84% at age 5 years), especially in those requiring mechanical ventilation or with B6-dependent seizures (increases in survival from 5% to 76% and 0% to 77%, respectively).
Asfotase alfa is administered by the subcutaneous route, usually at a total dose of 6 mg/kg/week divided in 3 or 6 doses.\textsuperscript{10,11} The most frequent adverse events are local reactions at the site of injection, occasionally accompanied by local lipodystrophy.\textsuperscript{12} Although some patients develop antibodies to the protein, this has yet not been proved to have an impact on clinical outcomes.\textsuperscript{9} Adequate followup is essential to ensure appropriate dose adjustments and to detect potential adverse events. The dose must be adjusted as needed to fit the actual weight of the patient, as a suboptimal dose is associated with rapid clinical and radiographic deterioration.\textsuperscript{13} Patients must be monitored for the potential development of ectopic mineralization through regular performance of radiography, retinal examination and renal ultrasound. Ectopic mineralization can also occur in the vasculature.\textsuperscript{14}

**Surgical treatment**

Abnormalities resulting in neurologic pathology require followup, especially craniosynostosis. The need for surgery should be evaluated on a case-to-case basis. Treatment with asfotase alfa does not seem to offer any benefits in this area.\textsuperscript{9}

Surgery may also be required to treat fractures or skeletal deformities such as scoliosis. In case of bone fracture, prolonged loading may increase the risk of fracture healing failure.\textsuperscript{15}

**Conclusions**

- Hypophosphatasia is a rare hereditary disease of bone and mineral metabolism characterized by deficient serum TNSALP activity that leads to skeletal and dental hypomineralization and extraskeletal manifestations.
- The phenotypic spectrum ranges from potentially lethal early-onset forms to forms with a later onset with fewer and less specific manifestations.
- Diagnosis in patients in whom there is a strong suspicion of HPP due to clinical manifestations should be based on the detection of low serum TNSALP activity and radiographic abnormalities, the potential accumulation of TNSALP substrates and the findings of molecular testing, among others.
- The recent authorization of asfotase alfa for enzyme replacement therapy in patients with childhood-onset HPP has changed the approach to the management of this disease.

**Conflicts of interest**

The authors have no conflicts of interest to declare.

**Acknowledgments**

We thank Alexion Pharmaceuticals for providing logistic support for the meeting of the working group (although the authors have been solely responsible for the contents produced by the group) and Ogilvy Healthworld for providing editorial support.

**References**

Hypophosphatasia: Diagnosis and treatment