DOI: http://dx.doi.org/10.47829/JCMI.2020.5505

Journal of Clinical and Medical Images

Case Report ISSN: 2640-9615 | Volume 5

Hypophosphatasia: Another Possible Cause of Periarticular Swelling?

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Received: 06 Dec 2020
Accepted: 22 Dec 2020
Published: 26 Dec 2020

Citation:

Casalini E. Hypophosphatasia: Another Possible Cause of Periarticular Swelling?. Journal of Clinical and Medical Images. 2020; V5(5): 1-2.

1. Introduction

Hypophosphatasia is a rare genetic metabolic disease caused by mutations of the ALPL gene, which encodes the tissue nonspecific alkaline phosphatase (TNSALP). The most important HPP's biochemical marker are a low activity of the serum ALP, high urine PEA and serum pyridoxal phosphate (PLP) [1].

The HPP onset can occur at any age and its severity is very variable, from fetal death to the isolated adult dental pathology (odontohypophosphatasia). The incidence of the severe forms of HPP has been estimated around 1:300,000 births, while the incidence of the less severe forms is unknown.

The disease can be inherited both with an autosomal recessive modality (corresponding to rare and severe forms) or dominant (milder forms, more frequent but under-diagnosed) [2].

The genetic heterogeneity affects both the severe and mild forms: most of the mutations observed in the severe forms do not induce residual enzymatic activity; however, there are no ALP-level cutoffs for the distinction of the different forms [1].

The early identification of the disease is fundamental because the timely start of specific therapy (afosfatase alpha) allows to modify the prognosis [3-4].

2. Case Description

In February 2017, an 8-year-old male presented to our Emergency department with swelling and pain in his left ankle with no history of recent trauma or infection. His personal medical history and family history were unremarkable. The ankle's X-ray showed no signs of fracture.

The clinical examination showed swelling of the medial side of the supra-malleolar side of the left tibia. Laboratory tests showed normal blood counts, hepato-renal function, LDH, CRP. MSUS (Figure 1a) didn't show any sign of synovitis in the tibio-talar and subtalar joints or tenosynovitis. However, minimal irregularity of the distal metaphyseal bone profile of the tibia was evident, with associated mild hypoechoic thickening of the soft tissues above the bone profile. The MRI (Figure 1b and 1c) and CT scan demonstrated an ambiguous alteration of the signal from spongiosa and cortical bone of the distal tibial metaphysis, with periosteal harmonic reaction and hyperintensity and contrast enhancement of the periosteal soft tissues, in absence of new periosteal deposition. The bone biopsy only showed medullary bone and dense fibrous connective tissue with normal vascular structure and minimal chronic inflammatory infiltrate. Blood tests were repeated and showed a slight increase in the bio-humoral indices of inflammation (CRP 0.58 mg/dl, ESR 32 mm/1/h) and low ALP values were reported for age (59 IU/l, normal values 96-187 IU/l), with slight deficiency of 25-hydroxyvitamin D (14.4 ng/ml, normal values >20 ng/mL). Calcium and phosphorus values were normal but urinary calcium/creatinine ratio was increased (0.40). Considering the low ALP values, his past medical history was reviewed: the only remarkable element was a premature loss of his deciduous teeth, starting

from 3 years of age, while no fractures and fatigue were reported. These findings suggested a diagnosis of hypophosphatasia (HPP), confirmed by the finding of elevated urine phosphoethanolamine (PEA 83 umol / mmol CRE, normal values 4-10 umol / mmol CRE).

Subsequent genetic testing revealed homozygous mutation c.542C>T (p.Ser181Leu) in exon 6.

In August 2018, our patient had an epileptic seizure resolved spontaneously without the necessity of pyridoxine's bolus: the EEG showed asynchronous epileptogenic anomalies. The antiepileptic profilaxis hasn't been started at the moment.

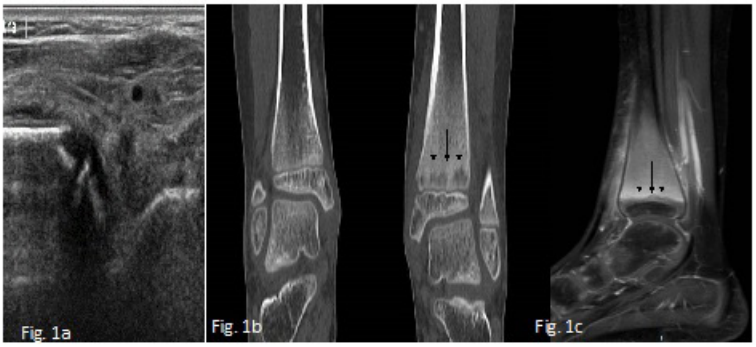

Figure 1a: Dorsal longitudinal scan of the left tibiotalar joint showing minimal irregularity of the distal metaphyseal bone profile of the tibia was evident, (see arrow-head).

Figure 1b & C: Sagittal Short TauI nversion MRI of the ankle showing an increasing signal intensity in the medullary bone of the distal tibial metaphysis, with periosteal harmonic reaction and hyperintensity of the periosteal soft tissues, in absence of new periosteal deposition.

3. Discussion

The clinical manifestations of HPP are variable: osteo-articular pain and walking difficulties are also reported, while periarticular swelling is not a typical HPP presentation. This case report suggests that a mild HPP form should be considered in the differential diagnosis of periarticular swelling with atypical metaphyseal abnormalities and mild periosteal soft tissues involvement. Other evocative elements include premature loss of deciduous teeth, but also a history of fatigue, hyporexia, poor growth, hypotonia and bone pain. Hypercalciuria may be present, causing nephrocalcinosis, while normal calcium and phosphorus levels don't exclude HPP. Serum ALP activity measurement is a simple, fast and not expensive nor invasive screening method for HPP. As previously outlined, its values should be interpreted according to age. ALP is not a specific marker and it may be lowered even in acquired conditions such as celiac disease, hypotiroidism, neuromuscular, infectious or neoplastic diseases. However, in case of repeated detection of a low ALP level combined with at least one clinical feature suggestive of HPP, other investigations should be performed, in particular urinary PEA and/or serum PLP measurement and eventually ALPL gene analysis.

The c.542C> T (p.Ser181Leu) mutation in ALPL gene was previously described in compound heterozygosis in a patient with an infantile form of HPP with residual enzymatic activity. No patient with this homozygous mutation has been described before in literature [5].

Seizures can occur in HPP, but they are more common in perinatal forms. In fact, ALP dephosphorylates a variety of substrates including pyridoxal phosphate (PLP), a cofactor in the synthesis of the neurotransmitter GABA. In HPP's seizures a PLP bolus can be efficacious to stop the seizure. In our patient, the occurrence of seizures in a juvenile HPP form and their resolution without the need for PLP treatment doesn't allow to consider them as a certain consequence of HPP. Since the clinical picture of our patient was mild, at the time we decided not to start enzyme replacement therapy with asfotase alfa, reserving us the right to reevaluate its indication in the future. In any case, a prompt diagnosis is important even in mild HPP form in order to avoid unnecessary and expensive further investigations and set-up an appropriate follow-up, including urinary calcium excretion monitoring and nephrocalcinosis prevention, periodical dental assessments and symptomatic treatment of articular and systemic manifestations.

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