Childhood hypophosphatasia with myopathy: clinical report with recent update

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ABSTRACT

Hypophosphatasia is a rare genetic disease with low tissue nonspeficic alkaline phosphatase activity (TNSALP), due to ALPL gene mutation. There are 6 clinical forms. Childhood form is caractherized by short stature, premature loss of decidous teeth and diffuse bone pain associated with a pathological bone fracture in the past. Laboratory findings present low serum level of alkaline phosphatase and high levels of serum and urinary extracelular metabolytes. It is described a case report of a 34 years old woman with previous diagnosis of childhood hypophosphatasia, caryotype 46,XX, and molecular screening for the gene ALPL with a c.1426>A p.E476K mutation, who complained of proximal muscular weakness intensified with the cold weather, exercise, and a waddling gait. The electromyography was compatible with myopathy but the muscle biopsy was normal. The serum creatine kinase levels were normal, as well as the others muscle enzymes. Clinical and laboratory//imaging dissociation is frequent in other metabolic bone diseases as osteomalacia. The rarity of this case of childhood hypophosphatasia with "*de novo*" non-progressive myopathy of the lower limbs, justified a case report with literature revision.

Keywords: Hypophosphatasia; Myopathy; Alkaline Phosphatase; Osteomalacia.

INTRODUCTION

Biomineralization is a process by which hydroxyapatite is deposited in the extracellular matrix (first within matrix vesicles that bud from the surface membrane of chondrocytes, osteoblasts and odontoblasts, and then followed by the propagation of the hydroxyapatite into the extracellular matrix and between collagen fibrils)[1]. Inorganic pyrophosphate (PPi) inhibits hydroxyapatite formation. Tissue-nonspecific alkaline phosphatase (TNSALP) hydrolyses PPi into phosphate (Pi), and this balance is fundamental to the mineralization[1-3]. There are 4 isomeres of the alkaline phosphatase (AP): TNSALP, intestinal, placenta and germ cell. All of them are homodimeric ectoproteins anchored to the plasma membrane by a phosphatidylinositol glycan (PIG) moiety. TNSALP clives PPi, pyridoxal-5-phosphate (PLP- an activated form of vitamin B_6) and phosphoethanolamine (PEA) in its dimeric form at physiologic pH, and whose expression changes according to the age[2].

Hyphosphatasia (HP) is a rare genetic disease caused by a low activity of the TNSALP with defective bone and teeth mineralization[4]. Clinical expression varies with the type of mutation and the age of diagnosis[1-4]. The incidence of the severe forms is estimated in 1/100000 (USA), but because its incomplete penetrance it is difficult to know the correct prevalence. *ALPL*, the gene encoding TNSALP, presents more than 190 mutations, some of them target specific populations or regions[2,4], and with a good genotype-phenotype correlation[2,5,6]. There are 6 clinical forms: perinatal (lethal or benign), infantile, childhood, adult and odontohypophosphatasia (Table I)[1-4].

The childhood form is characterised by low bone mineral density and unexplained fractures, premature loss of deciduous teeth (beginning with incisors), short stature and delay in walking, bone pain (bone oedema), joint pain (condrocalcinosis and osteoarthritis develop with aging), pseudofracture in the lateral cortex of the femoral diaphysis (Looser zones), and sometimes a waddling gait[2-4]. Specific diagnostic clues are shown in Table I, but screening for mutations in *ALPL* is essential to confirm the diagnosis[4]. Childhood form does the differential diagnosis with rickets, osteogenesis imperfecta, dentinogenesis imperfecta, cleidocranial

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TABLE I. CLINICAL FEATURES OF HYPOPHOSPHATASIA

Type	Inheritance	Clinical features	Dental features	Diagnosis
Perinatal (lethal)	AR	Hypomineralization and osteochondral spurs	–	Radiographs, ultrasonography
Perinatal (benign)	AR or AD	Bowing of the long bones, benign evolution	–	Ultrasonographyd, clinical evaluation
Infantil	AR	Craniosynostosis, hypomineralization, rachitic ribs, hypercalciuria	Premature loss of the deciduous teeth	Radiographs, laboratory findings and clinical evaluation
Childhood	AR (frequent) or AD (rare)	Short stature, bone fractures/deformity, bone pain, waddling gait	Premature loss of the deciduous teeth (incisors)	1. Radiographs: Bowdler spurs, shortening of the long bones, low bone mineral density 2. Laboratory: low activiy of AP, serum and urinary elevation of PEA, PLP, PPi, normal phosphocalcium metabolism, normal parathormone and vitamin D levels 3. Bone biopsy: low mineralization of the cartilage, normal cells 4. Bone MRI: hyperemia and metaphyseal edema
Adult	AR or AD	Stress fractures: metatarsal, tibia; chondrocalcinosis	–	Radiographs, laboratory findings and clinical evaluation
Odontohypo-phosphatasia	AR or AD	Alveolar bone loss	Dental caries	Laboratory, clinical and dental evaluation

Legend: AR= autosomal recessive; AD= autosomal dominant; AP= alkaline phosphatase; PEA = phophoethanolamine; PLP = pyridoxal-5-phosphate; PPi = inorganic pyrophosphate; MRI = magnetic resonance imaging.

dysostosis, Cole-Carpenter syndrome, idiopatic juvenil osteoporosis and renal osteodystrophy[2]. Milder forms of hypophosphatasia pose a problem for an accurate diagnosis[7]. Symptomatic treatment is applied, with orthopedic management[1-5,8]. Positive response to teriparatide as been reported and enzyme replacement therapy (ERT) looks promising[7].

It is presented a case report of hypophosphatasia with myopathy and a literature revision.

CASE REPORT

A 34-year-old woman was referred to our clinic with difuse bone pain and myalgias of the lower limbs and of the pelvic girdle that lasted for 10 years. Two years before she started with mild proximal muscle weakness in her lower limbs and pelvic girdle, with difficulty in walking and inability to climb stairs. She also complained of morning muscle stiffness for more than an hour. Her complaints intensified with physical demanding activities and with cold weather. She presented previous history of early delivery at 30 weeks, growth retardation, dental caries, pathologic coccyx fracture and the diagnosis of childhood hypophosphatasia (caryotype 46,XX; autosomal recessive; mutation c.1426G>A p.E476K heterozygote – Institut für Humangenetik, Universitatsklinikum Schleswig-Holstein, Kiel, Germany) when she was 20 years old.

The physical examination revealed short stature (weight 48 Kg; height 140 cm) (Figure 1), shortening of the 4th metatarsals, mild (grade 4/5) proximal muscle weakness in the lower limbs with difficulty in getting off the floor and in climbing stairs and a waddling gait. Deep tendon reflexes were normal and the muscles were not tender.

Serum AP showed low levels (28 U/L) without other abnormality in the muscle enzymes. Serum, urinary and immunologic analysis were normal (PPi, PLP and PEA were not performed). Radiological examina-

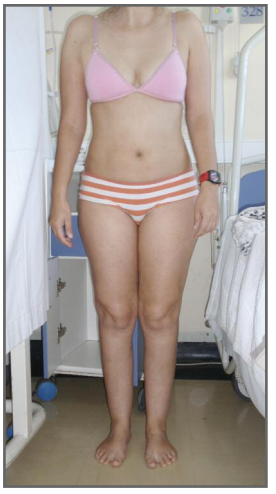

Figure 1. Short stature (weight 48 Kg and height 140 cm)

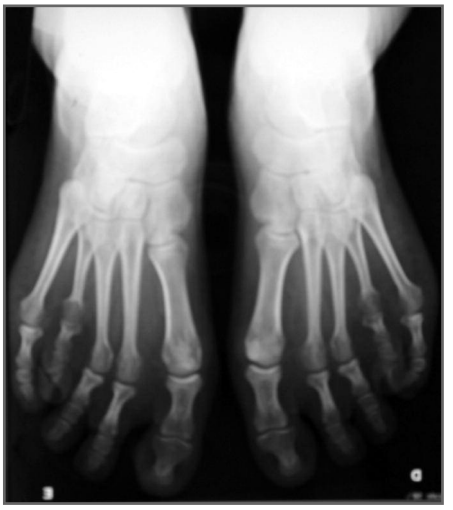

Figure 2. Feet radiograph with short 4th metatarsals

tion showed widening of the bone structures in the knee joint, shortening of the 4th metatarsals (Figure 2) and acetabular dysplasia (Figure 3). Electromyography of the lower limbs showed spontaneous fibrillations, polyphasic and low amplitude motor action potentials. Muscle biopsy specimens of the left quadriceps were examined by light microscopy and histochemistry, showing freezing artefacts, periferic nucleus, type I muscular fibres predominance, with normal diameter. The image was not available by the pathologist and the patient refused another biopsy for the muscular enzymatic study and the electron microscopy analysis. Mucopolysaccharidoses were excluded by lysosomic studies. Bone densitometry study

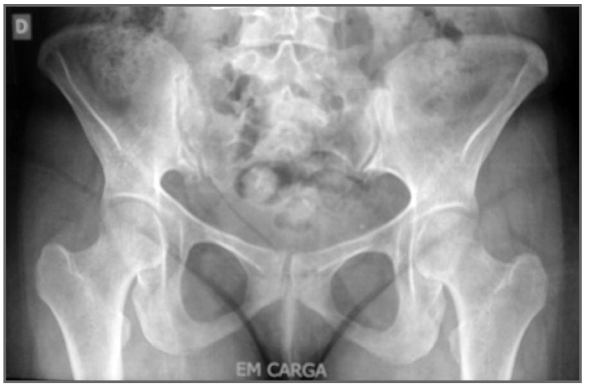

Figure 3. Hip radiography with acetabular dysplasia

showed cortical osteoporosis (T-score: -2,5) and lumbar vertebral magnetic resonance imaging was normal.

The patient was diagnosed with myopathy associated with metabolic bone diseases. She started on symptomatic treatment with vigilance of stress fractures, pseudofractures and dental care. The cortical osteoporosis was treated with teriparatide.

DISCUSSION

We describe a case report of a woman with the previous diagnosis of childhood hypophosphatasia who complains of myalgias and severe diffuse bone pain of the lower limbs for 10 years . Symptons of "*de novo*" myopathy of the lower limbs and pelvic girdle began 2 years ago. The radiologic and biochemical findings were characteristic of hypophosphatasia. The electromyography of the lower limbs showed myopathy, but the biopsy did not showed pathognomonic alterations. The bone densitometry study showed cortical osteoporosis. We explored the myopathy etiology in this patient. Adults with myopathy usually present proximal and symmetric muscle weakness, myalgias at rest, exercise intolerance, serum elevation of creatine kinase (CK) or myoglobinuria. The patient had typical symptons of myopathy: weakness, myalgia and stiffness. Her symptons worsened with demanding metabolic exercises but sometimes persisted even in rest periods.

First it was excluded non-neuromuscular episodic or persistent causes of weakness (hypotension, hypoxia, hyperventilation, hypoglycemia, anemia, infection, malignancy, malnutrition, hyperthyroidism, hyperparathyroidism, hypophosphatemia)[9].

Investigation for causes of proximal muscle weakness (inflammatory, drug and toxin-induced, infections, metabolic, muscular dystrophies, muscle channelopathies, neoplasm) were negative[9].

Polymyositis, dermatomyositis, inclusion body myositis and connective tissue diseases were excluded by the clinical, biochemical and hystological findings. She had no sarcoidosis or Behçet clinical features. She had no history of drugs with the potential of inducing the symptons and no history of previous infection.

Although the enzymatic muscle study was not been performed, her symptons were not compatible with glycogen storage diseases (e.g. rabdomyolisis with exercise, relieve at rest, normal electromyography, positive PAS byopsy and low serum lactate after exercise), with lipid storage diseases (e.g. rabdomyolisis, byopsy stained by Sudan red and high levels of serum lactate after exercise and in fasting) or mitochondrial myopathies (e.g. abnormalities of the oxydative metabolism, myoglobinuria, systemic symptons, palpebral ptosis, seizures, retinopathy, ophthalmoplegia, cardyomyopathy)[9,10]. Endocrine, nutritional and electrolyte disorders were excluded. Neuropatic conditions typically manifest with asymmetric weakness, distal involvement, sensorial alterations or abnormalities in the cranial nerves function. Muscular dystrophies were less likely by the biopsy, electromyography and the normal neurologic examination in facial, palpebral and upper limbs muscular strengh[9].

Finally it was selected the only characteristic that could associate the patient complains with specific diagnosis: myopathy associated with rest pain. In this case we considered childhood dermatomyositis, hypothyroid myopathy, drug-induced myopathy, infectious myopathy, myopathies associated with metabolic bone diseases and carnitine palmitoyl transferase deficiency. From the previous discussion the most likely cause is myopathy associated with metabolic bone diseases.

The most similar metabolic bone disease with reported myopathy is osteomalacia. Although the biochemical and biopsy findings are different between hypophosphatasia and osteomalacia, clinical symptons, radiologic findings and myopathy caractheristics are similar (Table II). Muscle fibres depend on 4 metabolic processes to replenish adenosine triphosphate stores during exercise: the CK reaction, glycogenolysis, oxidative phosphorilation and adenylate kinase and myoadenylate deaminase reactions[9]. Considering the osteomalacea myopathy[9,11,12] and concerning that this patient with hypophosphatasia has the same complains it was formulated 2 hypothesis for its etiology: low intramuscular levels of phosphate would difficult glycolysis during demanding metabolic situations and/or a possible low intracellular calcium intake by the sarcoplasmatic reticulum probably by low activity of vitamin D in the myocytes. Even with normal levels of serum vitamin D it must be assured that its actions in the myocytes is complete or is deficient.

Hypophosphatasia treatment is symptomatic. Anti-inflammatory non steroid drugs (AINEs) appear beneficial in bone pain, blocking prostaglandins (PGs) synthesis for a long period of time and suppressing the bone oedema[8]. Girschick *et al*, supports that PGs elevation in HP might be explained by the impaired clea-

TABLE III. CLINICAL FEATURES OF HYPOPHOSPHATASIA AND OSTEOMALACIA

Osteomalacia	Hypophosphatasia
Serum AP high levels	Serum low AP levels
Low vitamin D serum level and PTH elevation	Normal serum levels of vitamin D and PTH
Hypercalcemia, hypophosphatemia	Normal serum levels of calcium and phosphate
Biopsy: descontinuous atrophic changes in the muscle fibres, loss of myofibrils, type II fibre atrophy.	Biopsy: no atrophic signs, peripherical nucleus, type I fibre predominance.
In both	
Similar radiologic abnormalities	
Muscle hypotonia	
Waddling gait	
Diffuse bone pain worse with the cold and the exercise	
Proximal muscular weakness of the pelvic girdle and the lower limbs	

Legend: AP = alkaline phosphatase; PTH = parathormone

rance of calcium pyrophosphate resulting from alkaline phosphatase deficiency. PGs can reduce physical activity in these patients, thus AINEs may improve exercise tolerance and bone mineralization[8]. The cortical osteoporosis was treated with teriparatide (during 18 months) with improvement of the pain complains, together with calcium 1g/d and vitamin D 800 UI/d (increases the number of type II fibres with gait stabilization and prevention against falls).

Vigilance of serum and urinary calcium levels must be done once parathormone and vitamin D levels are normal. In these patients the bisphosphonates are avoidable as they have a similar conformation to PPi and inhibit bone mineralization. Teriparatide seems to upregulate wildtype *ALPL* gene expression, to reduce bone pain, to increase AP serum activity and to improve biochemical markers of bone turnover. Published data support our decision[13,14].

Glucosamine sulfate 1500mg/d may prevent secondary osteoarthritis[13]. Low impact exercises are important to improve muscle mass and maintain the mechanical stimuli that avoids the acute loss of bone in the muscle paralysis. Gross TS[15], published that acute response to transient muscle paralysis is due to a RANKL mediated osteoclastic activation and that it is restricted to the affected limb. Vigilance of stress fractures, pseudofractures and dental care are mandatory[2].

ERT has been developed and tested in mouse and clinical trials soon will be available to patients[2]. Millan and colleagues showed that ERT with a semi-synthetic bone-targeted form of TNSALP can prevent bone abnormalities of HP in the mouse[7]. Allogeneic transplant of human mesenchymal stem cells in the child (allogeneic cultured osteoblasts and bone fragments from crushed iliac bone; allogeneic HLA-matched T-cell-depleted marrow; allogeneic heterogeneous population of marrow cells and bone fragments) by intravenous administration resulted in clinical and radiologic evidence of bone mineralization, some patients began to walk or run, and one child turn its phenotype to mild HP[3].

In childhood HP the physician must perform a regular vigilance of the bone fractures, dental caries, serum and urinary calcium levels, vitamin D serum levels and general clinical examination. Foot orthotics may help in the management of the tarsal fractures in adults[2]. This form of HP presents a better prognosis than HP perinatal and infantil[1-5].

This patient improved her symptons and keeps a regular follow-up in the rheumatology department.

This report shows that a non-progressive proximal myopathy with muscle pain and stiffness may be an early sign of an osteomalacic syndrome.

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