Severe scoliosis in a Colombian patient with childhood hypophosphatasia

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Summary

Hypophosphatasia (HPP) is a rare inherited disorder of bone and mineral metabolism. In this report, we describe the clinical manifestations and the molecular analysis of a Colombian patient with childhood HPP. In this patient, a homozygous c.892G>A (p.E298K) mutation was detected in the *ALPL* gene. At 7 years of age, the right thoracic curve measured 30°, which progressed to 40° by the age of 9 years. To our knowledge, only few cases of scoliosis have been reported in HPP. Given this association, we suggest to consider the diagnosis of HPP in all patients with idiopathic infantile scoliosis of rapid progression.

KEY WORDS: case report; hypophosphatasia; scoliosis; Latin America.

Introduction

Hypophosphatasia (HPP; OMIM #241500, 241510, 146300) is a rare inherited disorder of bone and mineral metabolism, first described by Rathbun in 1948 (1). It is caused by various defects in the *ALPL* gene, located on chromosome 1p36.1 and which encodes the tissue-nonspecific alkaline phosphatase (TNSAP). HPP is generated by the elevated concentrations of the substrates for (2). Until now, more than 330 mutations in the *ALPL* gene have been identified, with most of them being missense point mutations (http://www.sesep.uvsq.fr/03_hypo_mutations.php) and the marked allelic heterogeneity results in clinical heterogeneity. The symptoms of this disease vary widely and are classified into five major categories depending on the age at diagnosis: perinatal (MIM241500), infantile (MIM 241500), childhood (MIM 241510), adult (MIM 146300), and odontohypophosphatasia (OHPP, MIM146300) (3). Autosomal recessive and autosomal dominant inheritance of these defects generally explain severe and mild forms of HPP, respectively (4). Some mutations exert a dominant-negative effect, helping to explain instances of autosomal dominant inheritance of HPP (5). While the penetrance of the disease in recessive HPP is assumed as complete, in dominant forms the penetrance may vary from a mutation to another one, and even from one patient to another with the same mutation (6).

Perinatal HPP, which manifests *in utero* and at birth, is nearly always fatal (7, 8). There is a profound skeletal hypomineralization, which is reflected as caput membraneceum and limbs that are short and deformed (9). Skin-covered osteochondral spurs may be seen protruding from the midshaft of forearms or legs (10). Other symptoms include pyridoxine-dependent seizures, periodic apnea and sometimes hypoplastic lungs (11). The benign prenatal HPP has been described in patients with bone deformity *in utero* that improve postnatally, with a clinical course ranging from infantile HPP to odontohypophosphatasia (12). The patients with infantile HPP presents the disease before 6 months of age (9). Progressive deformity of the thorax, rib fractures and tracheomalacia, fractures and bone deformities can accompany progressive skeletal demineralization. Clinically, patients can present wide fontanels, proptosis, mild hypertelorism and brachycephaly. Poor feeding, failure to thrive, or weakness with delayed motor milestones accompany signs of rickets. Hypercalcemia and hypercalciuria, resulting from blocked mineral entry into the skeleton, can cause vomiting and sometimes nephrocalcinosis and renal compromise (8, 9, 13). It has been estimated that ~50% of babies with infantile hypophosphatasia die in infancy (4, 9). Childhood HPP presents after 6 months of age with a wide-ranging expressivity (4, 13). Premature loss of some deciduous teeth. Rickets causes short stature and the skeletal deformities may include bowed legs, enlargement of the wrists, knees, and ankles as a result of widened metaphyses (14). Low bone mass, and recurrent, poorly healing fractures (15). In adults, the clinical expression and severity of HPP are highly variable (16), present initially with clinical manifestations suggesting osteoporosis, such as recurrent fractures and low bone mass, along with ill-defined musculoskeletal pain (17). Loss of adult dentition is common, recurrent metatarsal stress fractures eventually fail to heal, femoral pseudofractures that usually occur proximally and laterally in the subtrochanteric region (7, 18). Adult HPP can become debilitating due to recurrent fractures, skeletal and joint pain and muscle weakness (9). Finally, in the odontohypophosphatasia form, early loss of deciduous teeth, short root anomaly and dysplasia of dentin or cementum is not accompanied by any other clinical manifestations (19). Radiological studies and bone biopsies reveal no signs of rickets or osteomalacia (20).
The overall incidence of HPP is unknown. For severe forms it has been estimated at 1/100.000 in Canada (21) and 1/300.000 in Europe (22). The incidence of milder forms remains difficult to estimate, being possibly as high as 1 in 6.370 (22).
HPP is diagnosed in the presence of a medical history, physical examination, routine laboratory studies and radiographic findings consistent with the diagnosis (9). A reduced enzymatic activity of TNSALP measured on a blood sample is the key marker of the disease (23) and serum levels must be interpreted using reference ranges that are age- and sex-spe-

cific (24). Although HPP can typically be diagnosed without a mutation analysis of the ALPL gene (4), this information is crucial for documenting the inheritance pattern, for genetic counselling and prediction of recurrence risk and for prenatal diagnosis (9).
In this report, we describe the clinical manifestations and the molecular analysis of a patient with childhood HPP. To our knowledge, only few cases of scoliosis have been reported in HPP.

Case report

The proband is a 9-year-old female of Colombian origin, who is the youngest of three children and was born after a term pregnancy of 39 weeks. Her parents, 49 (father) and 38 (mother) years old, were healthy and consanguineous. She weighed 3.3 kg (50th percentile) at birth.
At the age of 8 months, the mother evidences deformity in column and thorax, she receives a diagnosis of idiopathic scoliosis and initiates controls and management by orthopedics. At an age of 2 years, she was evaluated by a geneticist that gave a diagnosis of metaphyseal dysplasia. An early loss, at 2 years, of deciduous teeth was reported and at the age of 5 years, due to the progression of deformity, a management with corset began. A surgical management was considered due to the progression of scoliosis and pain. No seizures, fractures or regression in neurodevelopment were observed.
The physical examination showed a height of 120 cm (-3.25 SD), a weight of 20 kg (-3.4 SD), and a head circumference of 50 cm (-2.30 SD), with normal teeth. The following signs were observed: costal depression in the left hemithorax, *pectum carinatum*, asymmetry of scapulae, severe scoliosis and left thoracic gib. Her blood calcium, phosphorus, and parathyroid hormone levels were normal. There were no aminoacids or mucopolysaccharides in her urine analysis and the serum ALP activity was low (27.4 IU/liter; normal, 156-359 IU/liter) (Table 1).
At 7 years of age, the right thoracic curve measured 30° (Figure 1), which progressed to 40° by the age of 9 years (Figure 2). Radiographs of long bones documented that the proximal and distal metaphyses were significantly widened, with hypomineralized regions and physeal widening. A homozygous c.892G>A (p.E298K) mutation was detected in the *ALPL* gene.
Her mother had a borderline serum alkaline phosphatase level (44 IU/liter) and was heterozygous for the p.E298K mutation. A bone mineral density scanning of the mother reported a normal Z score and the levels in the proband´s sister were normal. They have no known family history of HPP.

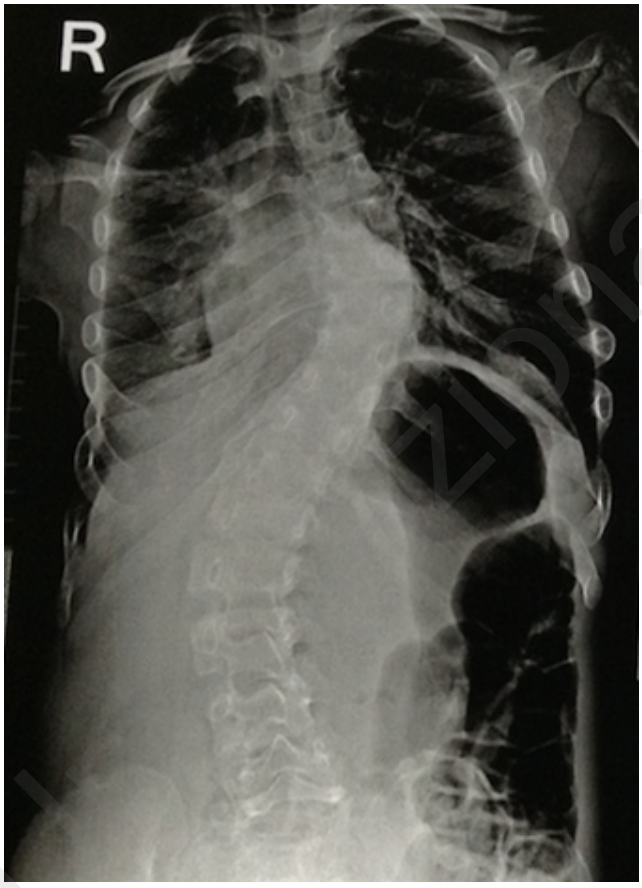

Figure 1 - Spinal X-ray (2013): left scoliosis with a Coob angle of 30°.

Discussion

Hypophosphatasia is an inherited form of rickets or osteomalacia, resulting from more than 300 mutations in the *ALPL* gene, which encodes TNSALP (25, 26). Although the expression of the disease is extremely variable, it always involves a defect in the mineralization of the bone and teeth. The onset of childhood HPP is after the age of 6 months and before adult life, having a particularly wide-ranging expressivity, which is now classified as mild or severe (4, 13). Premature loss of one or more primary teeth is an almost constant finding (13).
In the context of the pathophysiology of HPP, the primary biochemical defect is a deficiency of TNSALP catalytic activity, which leads to elevated circulating serum levels of inorganic pyrophosphate (PPi) and pyridoxal-5-phosphate (PLP), and to elevated urine levels of PPi and phosphoethanolamine

Table 1 - Results from laboratory tests.

Laboratory Test	Result	Reference Values
Alkaline Phosphatase	27,4 U/L	156-359 U/L
Ionized Calcium	10 mg/dL	8,5-10,2 mg/dL
Phosphorus	6,4 mg/dL	2,5-4,5 mg/dL
Parathyroid hormone	40,9 pg/mL	8-51 pg/mL
Vitamin D25	28,3 ng/mL	30-80 ng/mL

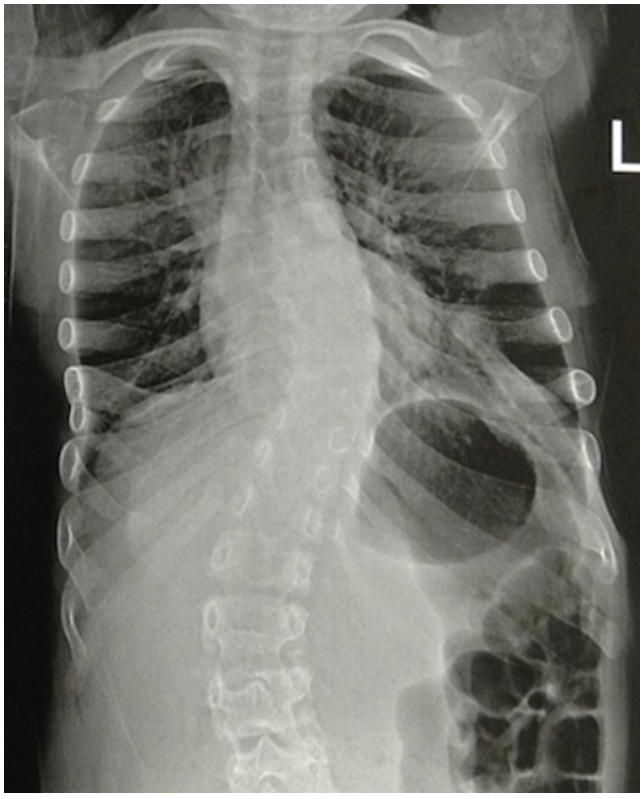

Figure 2 - Spinal X-ray (2015): left scoliosis with a Coob angle of 40°.

(PEA); all these molecules are considered as substrates of TNSALP (14). In the absence or reduced activity of the TNSALP enzyme, increased PPi levels in the bone matrix are the cause of rickets and osteomalacia and it results in HPP (27). PLP is the biologically active form of vitamin B6 and serves as a coenzyme in reactions that involve the catabolism of various amino acids and in the decarboxylation reactions necessary for the generation of several neurotransmitters (14). TNSALP hydrolyzes PLP to form pyridoxal (PL) and the accumulation of this metabolite is a possible factor in epileptic seizures (27). PEA has been found elevated in the urine of patients affected with hypophosphatasia (28) and its processing by TNSALP needs further study (27).

We described a 9-year-old female patient with childhood HPP, who presented the initial manifestations of the disease at 8 months of age. This case is similar to those reported by Arun (29) and Whyte (30). The first had a severe autosomal recessive variety of infantile hypophosphatasia but scoliosis became manifest clinically only at the age of 9 months; in the second case the patient developed scoliosis with rachitic rosary at the age of 7 months. The curve progression in these cases was more similar to progressive idiopathic infantile scoliosis than to neuromuscular scoliosis (29) and these previously described patients received surgical management. In these cases, the surgical techniques used and the choice of implants were not different when compared with other children with early onset scoliosis. However, our patient has received enzyme replacement therapy for 1 year and after an improvement in her bone mineralization, she will undergo surgery.

To our knowledge, only four cases of scoliosis associated with hypophosphatasia have been reported. In all these cases of HPP, the scoliosis appeared early in the first year of life and the subsequent progression was very rapid. This suggests that scoliosis is part of the clinical manifestations of the disease and not a phenomenon of “contiguous genes”, as it was previously postulated (29). Given this association, we suggest to consider the diagnosis of HPP in all patients with idiopathic infantile scoliosis of rapid progression.

Acknowledgements

The Author thanks Alexion Pharmaceuticals Colombia for its support with the process of revision and editing of the manuscript.

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