ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803–5253

CLINICAL OBSERVATION

Hypophosphatasia in a child with widened anterior fontanelle: lessons learned from late diagnosis and incorrect treatment

Angelika Mohn (amohn@unich.it)[1], Chiara De Leonibus[1], Tommaso de Giorgis[1], Etienne Mornet[2], Francesco Chiarelli[1]

1.Department of Paediatrics, University Hospital of Chieti, Chieti, Italy
2.Laboratoire SESEP, Centre Hospitalier de Versailles, Le Chesnay, France

Keywords
Calcium, Growth failure, Hypophosphatasia, Vitamin D, Widened anterior fontanelle

Correspondence
A Mohn, M.D., Department of Paediatrics, University Hospital of Chieti, Via dei Vestini 5, 66100 Chieti, Italy.
Tel: +39-0871-358015 |
Fax: +39-0871-574831 |
Email: amohn@unich.it

Received
20 October 2010; revised 22 December 2010; accepted 15 February 2011.

DOI:10.1111/j.1651-2227.2011.02228.x

ABSTRACT

Hypophosphatasia is characterized by deficiency of serum alkaline phosphatase with defective bone and teeth mineralization. We report on an 11-month-old boy who developed a complex clinical picture characterized by bulging anterior fontanelle, growth failure, nephrocalcinosis and impaired bone mineralization during high-dose calcium and vitamin D supplementation. This therapy had been started 5 months earlier for a presumed diagnosis of nutritional rickets established on the grounds of isolated widened anterior fontanelle. However, laboratory investigations revealed reduced alkaline phosphatase levels associated with hypercalcemia, hypercalciuria, low PTH and normal 25-hydroxy vitamin D levels. Genetic testing detected a compound heterozygote for the novel mutation (c.262G>A) and the described mutation (c.920C>T) in the ALPL gene.

Conclusion: High calcium and vitamin D supplementation should not be started in the presence of isolated signs of nutritional rickets without assessing calcium-phosphate metabolism. In fact, in rare bone-mineralizing disorders, this combined therapy might induce severe clinical complications.

INTRODUCTION

Hypophosphatasia is the inborn-error-of-metabolism caused by deactivating mutations within the gene that encodes the tissue-nonspecific alkaline phosphatase (TNSALP), leading to impaired bone and teeth mineralization. It manifests with a marked variability of clinical presentations ranging from the perinatal form with severe respiratory compromise to osteomalacia in adulthood (1). Clinical signs including widened anterior fontanelle, expression of bone hypomineralization, may overlap with those of other rare bone disorders implicating a complex differential diagnosis (2–5). However, in clinical practice, nutritional rickets is considered to be one of the most common causes of a widened anterior fontanelle (2). In fact, it occurs mainly in infancy as both breast and cow milk contain insufficient concentrations of vitamin D (6). For this reason, international guidelines have recommended a supplementation of 400 IU daily of vitamin D and an adequate dietary calcium intake in all infants during the first year of life (7).

We describe a child with hypophosphatasia where a widened anterior fontanelle has been misinterpreted as synonym of nutritional rickets and high-dose vitamin D and calcium supplementation had been started without establishing a precise diagnosis. During this therapy, he developed a complex clinical picture characterized by bulging of the anterior fontanelle, growth failure, nephrocalcinosis and diffuse bone lesions. This underlines the importance of a correctly conduced differential diagnosis considering even rare bone diseases, such as hypophosphatasia, in children presenting with common clinical signs.

CASE REPORT

An 11-month-old boy was admitted in January 2009 for the evaluation of bulging anterior fontanelle and growth failure which he had developed with high-dose vitamin D and calcium supplementation. Pregnancy and birth were unremarkable, and anthropometric measurements were normal. From birth, the boy had been exclusively bottle-fed and supplemented with vitamin D (400 IU daily). He grew normally for the first 6 months of life after which, because of the persistence of a widened anterior fontanelle (5 × 5 cm), vitamin D was increased to 600 IU and calcium supplementation was started (200 mg daily). As no improvement occurred after 1 month, calcium treatment was doubled leading to a daily intake of 1160 mg (760 mg daily contained in the artificial milk and 400 mg daily of supplementation). With this therapeutic regimen, he presented immediate ponderal growth failure and bulging anterior fontanelle. At the age of 8 months, oral therapy was stopped and calcium-phosphate metabolism was assessed for the first time showing increased calcium (2.87 mmol/L, normal range 2.10–2.55) and phosphate values (2.13 mmol/L, normal range 0.81–1.45), reduced PTH (4 ng/L, normal range 10–65) and high 25-hydroxy vitamin D levels (187.4 nmol/L, normal range 35–150). Moreover,

hypercalciuria (0.16 mmol/kg/24 h, normal value <0.1) and elevated calciuria to creatininuria ratio (0.57 mmol/mmol, normal value <0.37) were detected. Alkaline phosphatase serum levels were not assessed.

No further evaluations were performed until the age of 11 months when he was admitted to our hospital for the persistence of the clinical symptoms. On examination he showed markedly reduced weight (−3.53 SDS) with normal length and head circumference. With the exception of bulging anterior fontanelle, no further abnormalities suggestive for rickets were detected on physical examination. Blood tests confirmed the previous findings except for normalization of 25-hydroxy vitamin D levels. In addition, alkaline phosphatase levels were markedly reduced (30 U/L, normal range 70–110). A radiograph of arms, legs and skull documented severe and generalized osteopenia with tongues of radiolucency in distal metaphysis of radius and ulna (Fig. 1A), in peroneal and tibial epiphysis and the persistence of opened anterior fontanelle. Renal ultrasonography showed bilateral medullary nephrocalcinosis (Fig. 2A).

Because of the markedly suppressed alkaline phosphatase levels, a working diagnosis of hypophosphatasia was made and a low calcium diet was started (150 mg daily).

The ALPL gene encoding the TNSALP on chromosome 1p36.1 was sequenced, detecting a compound heterozygote for the novel mutation c.262G>A (p.E88K) from paternal origin and the maternal mutation c.920C>T (p.P307L) (8).

Over the following months, he presented ponderal catch-up growth (−1.78 SDS), normalization of all biochemical variables except for the persistence of low alkaline phosphatase levels. Furthermore, bone lesions (Fig. 1B) and nephrocalcinosis (Fig. 2B) improved; however, he developed craniosynostosis and premature loss of deciduous teeth.

DISCUSSION

Hypophosphatasia represents a rare but potentially lethal disease in children (9). Depending on the age at diagnosis, six clinical forms are currently recognized: perinatal lethal, infantile, childhood, adult, odontohypophosphatasia and a rare benign prenatal form. However, these clinical subtypes generally overlap (3). The infantile form, classified among the severe types of hypophosphatasia, manifests within the first 6 months of life. It is characterized by the presence of an open fontanelle, rachitic deformities and premature loss of deciduous teeth with a first-year mortality of 50% (10). In infants who survive, there is often spontaneous improvement in mineralization and remission of clinical problems with the exception of craniosynostosis (11).

The initial clinical finding in our patient was the persistence of a widened anterior fontanelle. With the exception of congenital hypothyroidism and increased intracranial pressure, enlarged anterior fontanelle is typically the clinical

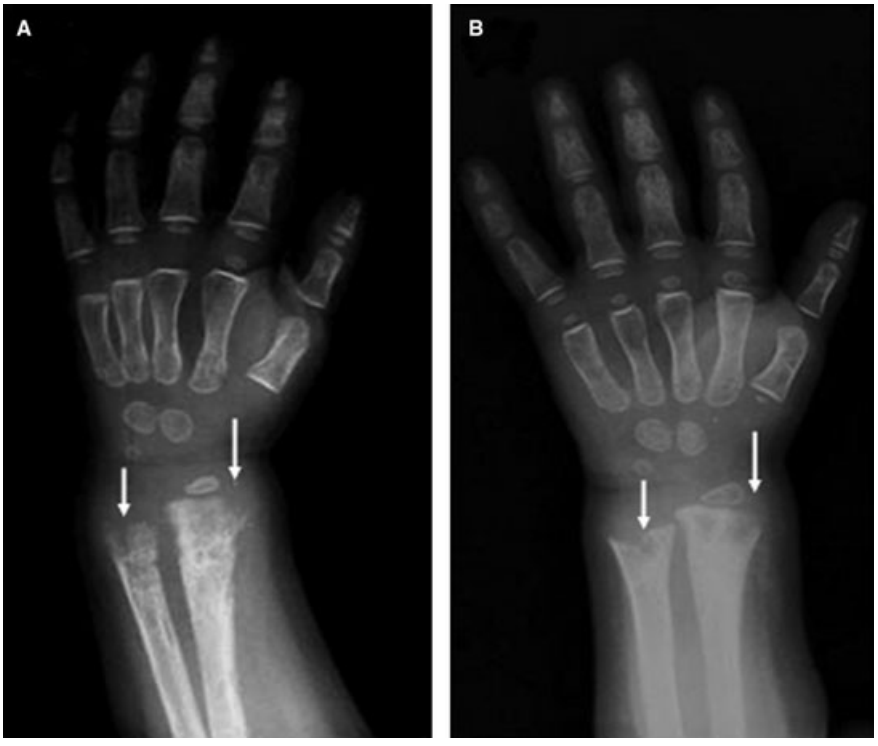

Figure 1 Radiograph of the left wrist and arm showing tongues of radiolucency (arrows) in distal metaphysis of radius and ulna before (A) and after low calcium diet (B).

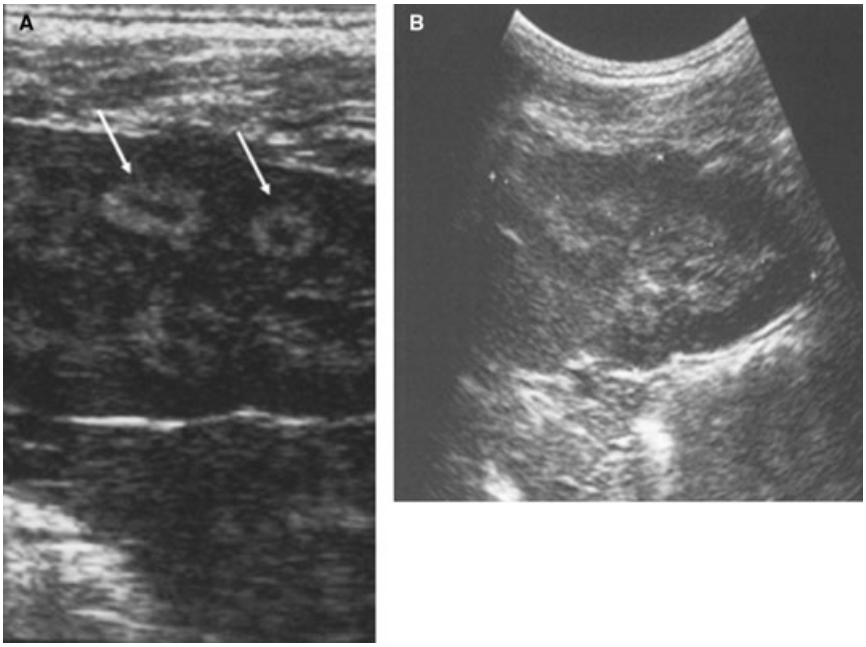

Figure 2 Renal ultrasound demonstrating bilateral medullary nephrocalcinosis (arrows) before (A) and after low calcium diet (B).

expression of a large spectrum of bone disorders (2). Nutritional rickets is the most common cause, estimated to be nine cases per 1 million children (12). However, within these bone-mineralizing disorders, hypophosphatasia, osteogenesis imperfecta and various clinical syndromes need to be considered especially in the presence of isolated signs of nutritional rickets (2). Differential diagnosis is not only based on the detection of clinical signs typical for each disorder but also on the assessment of calcium-phosphate metabolism combined with instrumental evaluation (Fig. 3). In contrast, in our patient, calcium and vitamin D supplementation has been started without previously evaluating calcium-phosphate metabolism presumably to prevent the development of further clinical signs of rickets. However, this therapeutic regimen led to rapid and severe deterioration of his clinical symptoms resembling vitamin D intoxication (13). In fact, the patient developed hypercalcemia with consequent growth failure because of anorexia and worsening of bone lesions induced by suppressed vitamin D serum levels. Moreover, owing to the increased excretion of calcium, he developed hypercalciuria leading to severe renal damage with medullary nephrocalcinosis detected in both kidneys. The combination of elevated vitamin D serum levels, bone hypomineralization and hypercalciuria was also suggestive of X-linked hypophosphatemia which was ruled out owing to high serum phosphate levels and vitamin D normalization 3 months after the therapy had been stopped (14,15). Both conditions, vitamin D intoxication and X-linked hypophosphatemia, present elevated alkaline phosphatase levels. In fact, the finding of reduced alkaline phosphatase levels in our patient raised the suspicion of hypophosphatasia. The lack of alkaline phosphate activity within the bone matrix blocks hydroxyapatite crystal formation leading to decreased uptake of calcium by the skeleton with progressive skeletal and dental demineralization and subsequent hypercalcemia (16,17). Our clinical suspicion of an infantile form of hypophosphatasia was confirmed on the basis of genetic analysis which showed a compound heterozygote for two different mutations within the ALPL gene encoding the TNSALP. On the basis of experimental data, the novel missense mutation from paternal origin explicates probably a moderate clinical effect associated with mild forms of hypophosphatasia. In contrast, based on *in silico* predictive models, the maternal mutation, already described in compound heterozygotes in cases of childhood or infantile hypophosphatasia (8), is probably highly severe.

Although the pathogenetic mechanism leading to the skeletal and dental defects is well understood, no curative treatment exists. At present, calcium diet restriction represents the first-line treatment to reduce the extracellular accumulation of calcium and subsequent hypercalciuria. In the present case, a low calcium regimen was associated with an improvement of both bone lesions and nephrolithiasis. However, severe vitamin D restriction has been reported to be associated with worsening of the metabolic bone disease (18).

Recently, a soluble form of human TNSALP has been created with a high affinity for hydroxyapatite crystals thanks to the addition of a repetitive C-terminal extension of 10 aspartate residues (19). This type of construct produces a modified TNSALP enzyme that displays high affinity for bone tissue *in vitro* and *in vivo*. Moreover, when injected daily in a TNSALP knockout mouse model of the infantile

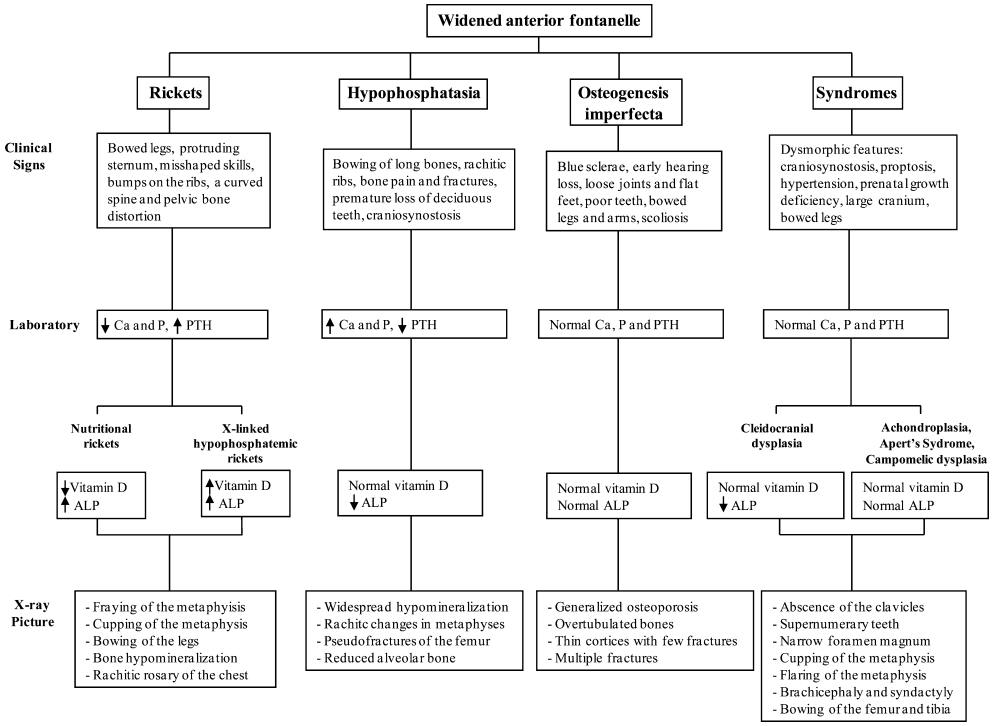

Figure 3 Differential diagnosis for isolated widened anterior fontanelle. Ca, calcium; P, phosphate; PTH, parathyroid hormone; ALP, alkaline phosphatase.

form of hypophosphatasia, this enzyme preserves skeletal mineralization and survival (20). More recently, as discussed in a preliminary report, 13 children have received the same therapy for 6 months showing an increase in alkaline phosphatase serum levels and presenting skeletal radiographic improvement with better muscle strength and mobility (21).

In conclusion, an isolated widened fontanelle should not be interpreted as synonym of rickets and in the absence of other specific risk factors, high calcium and vitamin D supplementation should not be started. In fact, our clinical case highlights the importance of first confirming the diagnosis as in rare bone-mineralizing disorders, this combined therapy might induce toxicity.

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