

## Mini Review Article

# Hypophosphatasia in adults

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Hypophosphatasia (HPP) is a sporadic inheritable disease. Patients suffer from defective bone and teeth mineralization, due to low levels of alkaline phosphatase (ALP). It is caused by mutations in the *ALPL* gene which encodes the tissue-nonspecific isoenzyme (TNAP or TRANSALP) of alkaline phosphatase. Hypophosphatasia is classified into six forms: lethal perinatal, benign prenatal, infantile, childhood, adult and odontohypophosphatasia. The adult form is the rarest and the mildest of all types characterized by low levels of alkaline phosphatase, increased levels of pyridoxal-5'-phosphate (PLP) in serum and increased levels of phosphoethanolamine (PEA) in urine. *ALPL* mutations associated with adult hypophosphatasia are either autosomal recessive or autosomal dominant. Patients' phenotype depends on the site of the enzyme these mutations affect. Although, there is not a treatment for this disease actually, enzyme replacement treatment (ERT) with asfotase alfa promises a lot to patients.

**Keywords:** ALPL gene, PEA, PLP, Alkaline phosphatase, Asfotase alfa**Introduction**

Hypophosphatasia is a sporadic inheritable disease first described by John Campbell Rathbun in 1948<sup>1,2</sup> in patients who presented with defective bone and teeth mineralization<sup>1,3</sup>, due to altered activity of alkaline phosphatase. According to the severity of symptoms and the age of the patients, hypophosphatasia is classified into six forms: perinatal (lethal), prenatal (benign), infantile, childhood, adult form and odontohypophosphatasia<sup>3</sup>.

Although several articles describe in detail the above-mentioned five of the six forms of hypophosphatasia, little is known about the adult form. In most references, adult hypophosphatasia is discussed through the parents of the proband suffering from more severe form of the disease. To the best of our knowledge, there is no reference in Greece yet. In this review, among the general features of hypophosphatasia, we discuss the current knowledge on the clinical and laboratory features of this rare form<sup>2</sup> of hypophosphatasia, which presents in middle age<sup>3</sup>.

**Etiology**

Alkaline phosphatase hydrolyses monophosphate esters in pH ranged between 8-10<sup>1</sup>. It is active only in its dimeric form after binding on some ions as cofactors, such as Zn<sup>2+</sup>, Mg<sup>2+</sup> and Ca<sup>2+</sup><sup>1,4</sup>. The enzyme plays a significant

role in bone and teeth mineralization, the process by which hydroxyapatite crystals are deposited in the extracellular matrix between collagen fibrils.

There are four isoenzymes: intestinal, placental, germ cells' and bone/liver/kidney<sup>1</sup>. The first three have restricted tissue expression and therefore are named "tissue-specific" with no role in mineralization. The last one is called "tissue-nonspecific" (TNAP or TRANSALP). It participates in the mineralization process and is compromised in hypophosphatasia<sup>1,4</sup>. Furthermore, TNAP hydrolyses pyridoxal-5'-phosphate (PLP) thus helping to release phosphate out of the cell<sup>4</sup>. PLP is one of the coenzymes of vitamin B<sub>6</sub>, which is used to transform glutamic acid to gamma-aminobutyric acid (GABA) in brain neuronal cells<sup>4-6</sup>. Reduced levels of TNAP lead to epileptic seizures in patients

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with hypophosphatasia because of lack of hydrolysed PLP in the neuronal cells<sup>1</sup>. Seizures in patients with hypophosphatasia may also be associated with increased intracranial pressure because of craniosynostosis<sup>1</sup>.

The tissue-nonspecific isoenzyme is encoded by the *ALPL* gene (ALP-Liver)<sup>7-9</sup> which is located on the short arm of chromosome 1 (1p36.1-34)<sup>1</sup>. Mutations in the *ALPL* gene lead to defective enzyme activity and thus to hypophosphatasia. Over 300 mutations have been described up to date<sup>1</sup>. Most of them are missense mutations. The increased number of genetic alterations and the different pattern of inheritance recorded (autosomal dominant or autosomal recessive) complicate the correlation with the clinical phenotypes<sup>1</sup>.

Hypophosphatasia follows either an autosomal or recessive pattern of inheritance. The severe forms of hypophosphatasia (perinatal lethal, infantile and childhood) are generally inherited by an autosomal recessive (AR) mode whereas the milder forms (adult and odontohypophosphatasia) follow both autosomal recessive and autosomal dominant (AD) trait<sup>4,10</sup>. In AR case there is a chance of 25% for an adult to develop hypophosphatasia while in AD cases the chance is raised to 50%<sup>11</sup>.

The gene associated with the disease is the *ALPL* including 12 exons<sup>3</sup> in a 50kb region<sup>1,12</sup>. Most mutations reported are missense (75,5%)<sup>13</sup> while other types of mutations acquire a lower frequency (small deletions 10,5%, splicing 6%, nonsense 4%, small insertions 2% and complex insertions/deletions, large deletions, and regulatory sequence mutations 1% or less)<sup>13</sup>.

## Incidence and prevalence

Today, the incidence of severe forms of hypophosphatasia is considered to be approximately 1/300.000 cases in Europe, while in Canada is 1/100.000 live births<sup>14</sup>. Moderate forms of the disease among Europeans account for 1/6.370 cases<sup>14</sup>. It is noticeable that in the United States, hypophosphatasia is more frequent among white people than among black people<sup>14</sup>, while in Africa, no case has been reported yet<sup>11</sup>. Hypophosphatasia has been reported in Hispanic and Chinese people and two TNSALP founder mutations are recognized to cause severe hypophosphatasia in the Japanese<sup>9</sup>.

## Clinical manifestations

As it has already mentioned, clinical features of hypophosphatasia depend on the form.

In the lethal perinatal form, patients have the most severe manifestations<sup>1</sup> as it is shown in utero and resulting in stillbirth or death soon after birth<sup>4</sup>. Infants who survive a few days have respiratory problems due to hypoplastic lungs and rachitic deformities of the chest<sup>2</sup>, apnea, seizures<sup>2</sup> and show shortened and deformed limbs<sup>1</sup> because of the poorly mineralized bones<sup>14</sup>.

However, in some cases, patients show a spontaneous

improvement<sup>2</sup> after birth (benign prenatal form)<sup>1,15</sup>. They have short and bowing limbs and often dimples overlaying the long bones deformities<sup>2</sup>, but some ultrasounds reveal progressive improvement of the skeletal deformities and mineralization during the third trimester of the pregnancy<sup>2</sup>.

In infantile form, patients may appear normal at birth<sup>2</sup>. The clinical symptoms of hypophosphatasia are generally less severe than the perinatal and appear before the age of six months<sup>1,15</sup>. Patients have respiratory complications due to rachitic deformities of the chest<sup>2</sup>. Increased intracranial pressure may occur despite of premature craniosynostosis<sup>2</sup>. Radiographs show rachitic changes in the metaphyses and widespread demineralization<sup>2</sup>. Patients may have hypercalcemia and hypercalciuria<sup>11</sup> which may lead to renal damage<sup>2</sup>. These symptoms may be reduced later in their lives. Without some kind of treatment, approximately, half of the cases die at the age of nine months<sup>15</sup>.

The childhood form, appears after six months of age and has milder manifestations<sup>1</sup>. Skeletal deformities, such as dolichocephalic skull and enlarged joints, short stature and waddling gait, a delay in walking are some of the clinical symptoms of this form<sup>2</sup>. Intracranial hypertension, fractures and bone pain may coexist as well premature loss of dentition, usually of the incisor teeth, is common<sup>2</sup>.

Odontohypophosphatasia is a dental disease without any other abnormalities of the skeletal system<sup>2</sup>. Patients lose their fully rooted teeth very early<sup>3</sup>. The anterior deciduous teeth, especially the incisors, are more likely to be affected<sup>3</sup>. Dental X-rays reveal reduced alveolar bone, enlarged pulp chambers and root canals<sup>2</sup>. Also, examination of teeth shows a reduction of cementum which is higher in the severe forms of hypophosphatasia<sup>11</sup>.

## Hypophosphatasia in adults Clinical and biochemical features

Hypophosphatasia patients' first symptom is, generally, a foot pain due to a stress fracture of the metatarsals<sup>16</sup> which sometimes is recurrent and poorly healing<sup>4</sup>. A thigh pain due to pseudofractures of the femur<sup>3</sup> (Looser Zones)<sup>11</sup> may also be a symptom. As mentioned above, only a few cases have been reported in adult hypophosphatasia. Women are more likely to develop hypophosphatasia than men whereas there are also young people among patients. Patients may have short stature<sup>3</sup> or they lose their mature dentition very early<sup>11</sup>. The presence of osteomalacia may help distinguishing adulthood hypophosphatasia from odontohypophosphatasia<sup>11</sup>. Skeletal deformities and dental problems are mentioned in half of the cases and they are relevant with the severity of the disease. Some patients present rickets and early loss of deciduous teeth in childhood<sup>3,16</sup>. Others suffer from chondrocalcinosis and pseudogout later in life<sup>3</sup>. Almost always women present low bone mass and crystal arthropathy<sup>15</sup>. Furthermore, histological examination of bones shows features of rickets with skeletal deformities while some histochemical tests on osteoclasts show absence of alkaline phosphatase activity<sup>11</sup>.

Case Report	Sex Age	Serum ALP	Serum PLP	Urine PEA	Serum PP <sub>i</sub>	Skeletal*	Dental**	References
1	F/23	4 (15-60U/L)	>250 (35-107nmol/L)	79.2 (<11.3μmol/mmol cr)	na	+	+	Macfarlane JD et al, 1992 Am.J.Med.Genetics <sup>22</sup>
2	F/<23	4 (15-60U/L)	>250 (35-107nmol/L)	82.6 (<11.3μmol/mmol cr)	na	-	+	Macfarlane JD et al, 1992 Am.J.Med.Genetics <sup>22</sup>
3	F/36	39↓	37↑	165↑	na	na	+	Hu JC-C et al, 2000 Eur.J.Oral Sci <sup>23</sup>
4	M/64	40↓	41↑	N	na	+	+	Hu JC-C et al, 2000 Eur.J.Oral Sci <sup>23</sup>
5	F/60	37↓	72↑	278↑	na	na	na	Hu JC-C et al, 2000 Eur.J.Oral Sci <sup>23</sup>
6	M/25	37↓	52↑	538↑	na	na	na	Hu JC-C et al, 2000 Eur.J.Oral Sci <sup>23</sup>
7	M/58	33↓	52↑	512↑	na	na	na	Hu JC-C et al, 2000 Eur.J.Oral Sci <sup>23</sup>
8	M/42	41↓	57↑	175↑	na	na	na	Hu JC-C et al, 2000 Eur.J.Oral Sci <sup>23</sup>
9	F/39	18 (30-120U/L)	na	↑	na	-	+	Herasse M.et al, 2003 J.Med.Genetics <sup>24</sup>
10	F/38	29 (47-147U/L)	na	na	na	na	+	Herasse M.et al, 2003 J.Med.Genetics <sup>24</sup>
11	F/na	32 (30-107U/L)	na	138 (20-100μmol/gr cr)	na	na	na	Herasse M.et al, 2003 J.Med.Genetics <sup>24</sup>
12	F/27	6 (30-110u/L)	na	na	na	+	+	Chou YY et al, 2005, Kaohsiung J.Med.Sci <sup>25</sup>
13	F/33	↓	↑	N	na	na	na	Luong KV et al, 2005, Am.Nutr.Metab <sup>26</sup>
14	F/64	↓	↑	na	↑	+	na	Khandwala HM, 2006, Endocr.Pract <sup>27</sup>
15	F/56	10-24 (40-150IU/L)	↑	na	↑	+	na	Whyte et al, 2007, J.Clin. Endocr.Metab <sup>18</sup>
16	F/53	6-8 (30-120IU/L)	>1000 (35-110nmol/L)	52 (5-18μmol/mmol cr)	na	+	+	Gagnon C et al, 2010, J.Clin.Endocrinol.Metab <sup>28</sup>
17	M/32	104 (115-359IU/L)	na	96 (29.1-75.6nmol/ mg cr)	na	+	-	Lida K et al,2012,J.Bone Miner.Metab <sup>29</sup>
18	F/43	↓	↑	N	na	-	-	Guanabens N et al, 2014, J.Bone Miner.Res <sup>30</sup>
19	F/50	↓	↑	N	na	-	-	Guanabens N et al, 2014, J.Bone Miner.Res <sup>30</sup>
20	F/53	↓	↑	N	na	-	-	Guanabens N et al, 2014, J.Bone Miner.Res <sup>30</sup>

\* : femur fractures, repeated fractures, pseudofractures, joints and periarticular pains, arthritis. \*\*: early loss of primary or permanent teeth. na: not available. N: normal value.

**Table 1.** Reported cases of hypophosphatasia in adults.

The biochemical findings of the disease as well as dental and skeleton manifestations of these patients are listed on Table 1. Generally, biochemical measurements show decreased levels of ALP in all patients, even though ALP reference values differ between studies. However,

under particular conditions such as pregnancy (last trimester), hepatobiliary disease, some orthopedic surgeries, and fractures the levels of ALP may be temporarily increased in serum<sup>14</sup> and therefore the diagnosis of hypophosphatasia may be confused<sup>14</sup>. This

problem can be resolved with quantitation of alkaline phosphatase's isoenzymes in serum<sup>14</sup>.

Other factor that may be indicative of the disease are the increased levels of phosphoethanolamine (PEA) in urine<sup>11,17</sup>. However, measurement of PEA is not pathognomonic<sup>6</sup>. As shown in Table 1, some cases show normal levels of PEA (cases 13, 18-20). Furthermore, levels of pyridoxal-5'-phosphate (PLP) in plasma are also elevated. This measurement is a sensitive indicator<sup>6,11</sup> and patients who take supplements of vitamin B<sub>6</sub> may have false increased levels of PLP<sup>6,11</sup>. It has been suggested that levels of inorganic pyrophosphate (PP<sub>i</sub>) in plasma may be increased in hypophosphatasia but it is not known whether this increase in plasma reflects accumulation of PP<sub>i</sub> in bones<sup>6</sup>. PP<sub>i</sub> levels are not available in most hypophosphatemic cases reported. We found only two cases in the literature with increased PP<sub>i</sub> levels. Measurement of PP<sub>i</sub> is not frequent and assays are carried out in research laboratories.

### Genotype-phenotype correlation

Several efforts have been made to establish a relationship between genotype and phenotype in hypophosphatasia, but it is not fully understood. Siblings have been reported with different phenotypes<sup>15</sup> and most patients have unique genotypes<sup>7</sup>. Generally, the severity depends on the region of the protein in which mutations have occurred<sup>1</sup>. Mutations found in the active region of the molecule are related to severe phenotype<sup>3</sup>. Furthermore, phenotype depends on the type of mutation at residues of the enzyme and the stability of the molecule<sup>1</sup>. Patients with mild hypophosphatasia carry at least one mutation that exhibits significant residual enzymatic activity, as it is shown when tested, while in severe hypophosphatasia patients carry mutations that usually do not product enzymatic activity<sup>2</sup>.

Some studies show that in severe cases of the disease the missense mutations produce a mutant protein that failed to reach the cell membrane. On the contrary, in mild hypophosphatasia the mutant protein is found to be partially correctly localized to the cell membrane<sup>2</sup>.

Although no clear genotype-phenotype relationship has been established, genetic analysis of the *ALPL* gene may help in the establishment of the diagnosis<sup>13</sup>, especially in the cases in which biochemical findings and clinical examination are inconclusive. The identification of a mutation in the *ALPL* gene helps distinguishing hypophosphatasia from other skeletal diseases such as osteogenesis imperfecta<sup>3</sup>, cleidocranial dysplasia<sup>17</sup>, osteoporosis (multiple fractures, low bone mass) and osteoarthritis (crystal arthritis)<sup>15</sup>. Furthermore, through genetic analysis it is easier to offer genetic counseling or perform molecular prenatal diagnosis to families affected by severe forms of the disease<sup>3,13</sup>. On the other hand, it should be noted that the presence of a mutation in the *ALPL* gene is not definitive for the development of hypophosphatasia, as other biochemical and/or clinical symptoms<sup>14</sup> should coexist.

### Treatment

There is no treatment that heals hypophosphatasia<sup>3</sup>. The aim of the current therapeutical approaches is supportive in order to relieve patients from the symptoms<sup>3</sup>. Babies who suffer from thoracic deformities can be relieved with mechanical ventilation<sup>18</sup> and children with severe scoliosis may be needed surgery<sup>18</sup>. Seizures depending on vitamin B<sub>6</sub> can be improved by taking supplementation of this vitamin and hypercalcemia with less dietary Ca<sup>9</sup>. Adults with femoral fractures or pseudofractures become better with load-sharing intramedullary fixation<sup>18</sup> and some other orthopedic technics in the ankle can help them with metatarsal fractures<sup>18</sup>. Treatment with non-steroidal anti-inflammatory drugs seems to have a sort of benefit in patients<sup>18</sup> while teriparatide seems to offer some temporary positive results in adult hypophosphatasia<sup>19-20</sup>.

Adults may, also, have a benefit taking therapy with parathormone (PTH)<sup>18,21</sup>. Doctors must be very careful using bisphosphonates because patients with hypophosphatasia may be worsen<sup>15</sup>.

Enzyme replacement therapy (ERT) with asfotase alfa seems promising a lot<sup>3</sup>. Asfotase alfa is made up of a soluble form of tissue-nonspecific alkaline phosphatase (TNAP) which continues having its enzymatic activity but its glycosylphosphatidylinositol anchor is extracted<sup>1</sup>.

Patients' treatment with asfotase alfa has improved the condition of the individuals as it is found in skeletal radiographs and pulmonary and physical function<sup>21</sup>. However, there isn't enough experience about its safety in treatment for a long time<sup>22</sup>. Nowadays, experiments with mice show that gene therapy using marrow cell transplantation or viral vectors carrying ALP may someday cure hypophosphatasia<sup>14</sup>.

### Conclusions

Hypophosphatasia is an inheritable bone disease characterized by bone hypomineralization. The diagnosis of the disease may be confirmed through mutational analysis of the *ALPL* gene which encodes the TNAP isoenzyme of alkaline phosphatase. All affected patients have diminished function of one or both of their *ALPL* alleles.

The symptoms of the disease vary depending on the clinical form. Patients with severe forms suffer from respiratory failure, which is the main cause of death.

The adult form is the rarest form of the disease and has milder manifestations. It occurs at middle age and characterized mainly by extremely low levels of ALP in serum, increased levels of PLP in plasma and PEA in urine. Patients suffer from some repeatedly fractures and pseudofractures and early loss of premature or permanent teeth.

Currently, there is no treatment for healing hypophosphatasia, however enzyme replacement therapy (ERT) with asfotase alfa seems promising.

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