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Editorial

Diagnosis and treatment of adult hypophosphatasia: Still a big challenge?

Hypophosphatasia (HPP) is a rare genetic disorder that presents variably in age of onset, symptoms, and severity. The disease was first described in 1948 by John C. Rathbun in a patient with rickets, seizures, and reduced alkaline phosphatase (ALP) activity in serum and bone tissue [1]. HPP is caused by loss-of-function mutation in the *ALPL* gene, resulting in low activity of tissue nonspecific alkaline phosphatase (TNSALP). Four genes encode ALP. Of the four, *ALPI*, *ALPP*, and *ALPPL2* genes are expressed in a tissue-specific manner in intestines, placenta, and germ cells, respectively. These three gene products are true isoenzymes that differ in amino acid sequences but share a high degree of homology more than 90%. The fourth *ALPL* gene encodes TNSALP protein, which is present in various tissues, including bone, liver, and kidney. TNSALP has much lower sequence homology than the other three ALP isoenzymes compared to the high homology among the three. Bone and liver isoforms of TNSALP are identical in the amino acid sequence but only differ in post-translational modification: they have distinct sugar chains due primarily to differences in O-linked glycosylation [2]. In healthy individuals, serum ALP is mostly derived from liver and bone. Bone ALP (BAP) can be measured by a specific assay and has been widely used as a bone turnover marker. In HPP patients, both total ALP and BAP are usually found to be low.

HPP has been classified based on age of onset into perinatal, infantile, childhood, and adult HPP. The fifth type of HPP is odonto-HPP that only affects teeth. Perinatal and infantile types of HPP are generally severe and the latter can be fatal. The patients often grow rachitic if they survived. HPP found in adulthood includes both the true adult-onset type HPP and survivors of milder forms of childhood-onset HPP. Diagnosis of adult HPP has been a challenge due to the lack of specific biochemical abnormalities as well as characteristic physical signs or symptoms. HPP in adults remains undiagnosed until approximately 10 years after the onset of symptoms [3].

In a previous issue of *Osteoporosis and Sarcopenia*, Kim et al. [4] reported 3 cases of adult hypophosphatasia (HPP) and summarized its pathophysiology, symptoms and treatment. The first case was a 25-year-old woman who presented with delayed healing after operation for hip dysplasia. She had pain and stiffness in her neck, back and hip, and weakness in her legs. She also complained of chronic fatigue and feeling of sickness. The second case was a 52-year-old woman referred for osteoporosis management due to low bone mineral density (BMD). Her BMD T score was −1.3 at lumbar spine and −2.7 at femoral neck. She had no complaints. The third was a 31-year-old female referred after being found to have low serum ALP activity without any apparent symptoms.

As typically seen in the three cases above, adult HPP patients often present with non-specific symptoms such as fatigue, generalized pain, and muscle weakness, or even with no complaints. A list of clinical manifestations associated with HPP in adults has been described [3]. Particularly, diagnostic clues have been reported to include: recurrent fractures, poorly healing fractures, chondrocalcinosis, nephrocalcinosis, enthesopathies with calcification of the insertion sites for tendons and ligaments, presence of musculoskeletal pain, abnormal gait, early loss of primary teeth with the root intact, and abnormal tooth color or shape [5]. Biochemically, due to decreased ALP activity, HPP patients show accumulation of ALP substrates, ie, increased serum PLP: pyridoxal 5′ phosphate (vitamin B6) and urine PEA: phosphoethanolamine, although the sensitivity and specificity of such measurements are not satisfactorily high as a definitive diagnostic test. Thus, low serum ALP is the most reliable and consistent biochemical abnormality. Osteomalacia caused by other diseases is characterized by high ALP, which is the opposite of HPP and makes it easy to distinguish from HPP. Physicians should however be aware that many drugs and pathological conditions including endocrine disorders, hematological diseases and nutritional deficiencies cause low ALP [5]. It is also of note that severity of the disease does not correlate with serum ALP activity, which is not necessarily below the lower limit of reference range.

Recently, the HPP International Working Group has proposed diagnostic criteria for adult HPP: major criteria include *ALPL* gene variant(s), elevation of natural substrates of TNSALP, atypical femur fractures, and recurrent metatarsal stress fractures, whereas minor criteria consist of poorly healing fractures, chronic musculoskeletal pain, early atraumatic loss of teeth, chondrocalcinosis and nephrocalcinosis. Persistently low ALP with 2 major, or 1 major and 2 minor criteria establishes the diagnosis of HPP [3,5,6]. It is somewhat surprising that the presence of *ALPL* gene variants is not a prerequisite for diagnosis. It may be clinically reasonable because *ALPL* gene variants have been identified only in 83% of the strongly suggestive cases [3]. Whether such patients have gene mutation in the non-coding region of the *ALPL* gene or in another functionally related gene is unknown. They did utilize the best knowledge of clinical signs and symptoms at that point to establish the diagnostic criteria. However, its reliability depends on the database of adult HPP patients, which is currently insufficient in size and quality. The authors acknowledged that our understanding of HPP will continuously evolve as adult cases of HPP accumulate, leading to the need to update the guideline probably within several years [3,5].

Why should adult HPP be diagnosed at all? The apparent reasons are twofold. First, we do have an effective enzyme replacement therapy by

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Asfotase alfa. Although limited, accumulating evidence suggests clinical and radiographical improvements of musculoskeletal signs and symptoms of adult HPP patients [7]. Case 1 in the paper by Kim et al. [4] also experienced pain relief and radiographical healing changes after starting treatment with Asfotase alfa. Whether such enzyme replacement therapy in milder forms of adult HPP is indeed useful and necessary remains to be determined. Cost-effectiveness will also be a matter.

Secondly, adult HPP could be mistreated as or complicated with osteoporosis as in Case 2 [4]. Although low ALP should result in impaired calcification of the bone, BMD of adult patients with HPP widely varies from normal to very low, but usually exhibits mild to moderate decline. And they often lack typical signs of osteomalacia. Paradoxically, accumulation of pyrophosphate may cause ectopic calcification in HPP. A big concern about the treatment of HPP patients with anti-resorptives is the occurrence of atypical femur fractures (AFF). A meta-analysis indicated that AFF occurred in up to 10% of patients with HPP [8]. And only one-third had received antiresorptive treatment, suggesting that HPP itself is a risk factor for AFF. Although the impact of anti-resorptive treatment is unknown, use of anti-resorptives, particularly bisphosphonates, should thus be avoided in HPP patients. Some case reports also described use of bone anabolic agents with inconsistent results as summarized in the paper by Kim et al. [4]. Thus, management of HPP bone changes is still a big challenge, and effect of anti-osteoporotic agents remains to be determined.

Conflicts of interest

Daisuke Inoue has received honoraria for lectures on hypophosphatasia from Alexion Pharmaceuticals, Inc.

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