Hypophosphatasia is a rare inherited metabolic disease characterized by rickets with reduced plasma and tissue alkaline phosphatase activity. It may be present in infancy, childhood, or adulthood. Various clinical manifestations reflect different forms of alkaline phosphatase gene expression. In this report, we present two cases of hypophosphatasia, one of the infantile and the other of the adult form. The infantile case presented with failure to thrive, hypotonia, and radiologic rickets at 4 months old. The adult case had repeated fractures and marked loss of bone density demonstrated by radiographs. Both cases showed extremely low levels of alkaline phosphatase. To the best of our knowledge, they are the first reported patients with hypophosphatasia from the Taiwanese population.

**Key Words:** hypophosphatasia, alkaline phosphatase


Hypophosphatasia is a hereditary disorder marked by a deficiency of alkaline phosphatase (ALP) activity in the liver, bones, and kidneys, and is associated with defective skeletal mineralization. It is caused by the loss-of-function mutations in the tissue nonspecific ALP gene (*TNSALP*), the gene encoding the isoenzyme TNSALP, which is located in the chromosome region 1p36.1–1p34 [1]. The large variation in clinical manifestations of the disease reflects the extent of the loss of enzyme function and may be indicated by a variety of symptoms and signs over a wide range of ages [2].

To the best of our knowledge, there are no previous reports of hypophosphatasia in the Taiwanese population. We describe two cases of hypophosphatasia, one of the infantile form confirmed by hypercalcemia and radiologic rickets, and the other of the adult form that presented with a history of premature loss of teeth and repeated fractures.

We discuss the clinical variation of the disease and the treatments adopted to control chronic bone demineralization.

**Case Presentations**

**Case 1**

A baby was referred at the age of 4 months for hypotonia, failure to thrive, and rickets. She was the second child born to unrelated parents without any family history of bone disease. She was born at full term with a birth weight of 2.45 kg. Poor feeding, vomiting, and hypotonia developed gradually. On examination, her body weight was 4.23 kg and body length was 54 cm, both below the 10th percentile. In addition, her head girth was 39.5 cm (10–25th percentile).

Physical examination showed widening of the anterior fontanel and generalized hypotonia. No blue sclera or short limbs were noted. Pertinent laboratory values were: serum calcium concentration, 2.9 mmol/L (normal, 2.05–2.55 mmol/L); phosphate, 1.52 mmol/L (normal, 0.74–1.52 mmol/L); intact parathyroid hormone, 1.14 pmol/L (normal, 1.1–5.3 pmol/L); ALP, 12 U/L (normal at 4 months, 50–260 U/L). Urinary measurements included a calcium/
creatinine ratio of 2.7 (normal, < 0.8). Roentgenograms showed poor mineralization of the long bones, most noticeable in the proximal femur and proximal humerus (Figures A and B). There was poor ossification of the epiphysis of bilateral distal ulnar, radius, and femur and proximal tibia. Cranial computed tomography (CT) showed decreased mineralization of the skull (Figure C). Renal ultrasonography revealed echogenic medullary pyramids consistent with nephrocalcinosis (Figure D). The diagnosis of hypophosphatasia was made and treatment with calcitonin and trichlormethiazide was started.

The baby was re-admitted at 5 months of age with pneumonia, fever, vomiting and respiratory distress. Serum calcium concentration was 2.3 mmol/L, phosphate was 1.13 mmol/L, and ALP was 26 U/L. She died 2 weeks later due to respiratory failure.

**Case 2**

This patient was referred to our endocrine clinic at the age of 27 years due to repeat fractures. No family history of metabolic bone disease was noted. Her history included the premature shedding of deciduous teeth at 3 years old and she had visited our dental department at the age of 17 for periodontitis, enamel hypoplasia, and malocclusion. She suffered right tibiofibular fracture when she was 23 years old and a left femoral fracture when she was 26 years old. Roentgenograms showed marked loss of bone density over the long bones. Bone mineral density (BMD) at the right femoral neck measured by dual-energy X-ray absorptiometry showed severe osteoporosis with a Z-score of −4.12. Laboratory investigations revealed a serum calcium concentration of 2.4 mmol/L, a phosphate concentration of 1.36 mmol/L, an ALP level of 6 U/L (normal adult, 30–110 U/L), and a 25-hydroxyvitamin D concentration of 49.25 nmol/L (normal, 35–150 nmol/L). The adult form of hypophosphatasia was diagnosed. No further fracture episodes were noted during the 3 years of follow-up at our clinic. Serial BMD measurements showed no significant improvement, despite the use of oral alendronate. Follow-up serum ALP was 5 U/L.

**DISCUSSION**

Hypophosphatasia was first described by Rathbun in 1948 [3], and since then, about 300 patients have been described throughout the world [4]. Six forms of hypophosphatasia have been identified [4]. The perinatal form is often lethal, owing to deformation of the chest wall and respiratory insufficiency, fractured extremities, and intracranial hemorrhage [5]. Infantile hypophosphatasia manifests before 6 months of age and patients appear normal until the onset of failure to thrive and rickets. The cranial sutures are wide, reflecting hypomineralization of the skull. A flail chest from rachitic deformity predisposes the infant to recurrent pneumonia, and renal complications are secondary to hypercalcemia, hypercalciuria, and nephrocalcinosis. The mortality rate is around 50% [4,6]. Childhood hypo-
phosphatase often presents with premature loss of deciduous teeth and may be associated with rachitic skeletal defects that occasionally show spontaneous improvement [6]. Adult hypophosphatasia is the least severe form, with a history of the premature loss of deciduous teeth followed by recurrent fractures secondary to osteomalacia. Some individuals do not develop clinically apparent skeletal disease [7]. Patients who develop only dental manifestations are regarded as having odontohypophosphatasia. An extremely rare variant, pseudohypophosphatasia, resembles infantile hypophosphatasia except that serum ALP activity is normal. Case 1 in this report is compatible with the diagnosis of infantile hypophosphatasia. The patient in Case 2 was healthy until she suffered two fractures in adulthood, which is compatible with the clinical course of adult hypophosphatasia.

It has been estimated that severe forms of hypophosphatasia occur in approximately 1/100,000 live births [4]. The milder childhood and adult forms are probably somewhat more common. Less affected hypophosphatasia patients may show only low levels of ALP in the blood and never suffer bone problems [4]. Thus, the prevalence of mild hypophosphatasia may be underestimated. A routine test for ALP should be used in patients with repeated fractures or premature exfoliation of deciduous teeth to detect mild forms of hypophosphatasia. Hypophosphatasia can be diagnosed with confidence in individuals with typical clinical histories, physical findings, and radiologic changes in whom serum ALP activity is clearly and consistently subnormal. Although hypercalcemia is relatively common in perinatal and infantile hypophosphatasia, it is uncommon in childhood and adult forms [8].

The primary pathophysiologic consequence in patients with hypophosphatasia is reduced TNSALP activity leading to the accumulation of its endogenous substrates, pyrophosphate, pyridoxal-5’-phosphate, and phosphoethanolamine, and to defective mineralization of skeletal osteoid [9]. The clinical severity of hypophosphatasia is related to the sites of mutation in the TNSALP gene. Molecular studies have shown at least 65 distinctive deactivating TNSALP defects among hypophosphatasia patients worldwide [10]. Perinatal and infantile hypophosphatasias are transmitted as autosomal recessive traits and can be attributed to homozygous or compound heterozygous mutations in the TNSALP gene. Subjects with childhood or adult hypophosphatasia can also be compound heterozygotes for TNSALP mutations. However, it seems possible that mild disease is transmitted as an autosomal dominant trait [4].

There is no established medical regimen for hypophosphatasia, although several therapies have been studied [10–14]. Enzyme replacement therapy by infusion of serum from patients with high ALP activity has limited benefit [13]. Bone marrow transplantation may be effective but requires further evaluation [14]. The administration of vitamin D or its metabolites is inadvisable because, even in small doses, these patients develop hypercalcemia easily. Therapeutic trials are made difficult by the variable clinical and radiologic course.

REFERENCES

台灣之先天性磷酸酶缺乏症 — 二病例報告

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先天性磷酸酶缺乏症為少見之代謝性疾病，其主要特徵為血清及組織之鹼性磷酸酶下降以及佝僂症。此病可發生於嬰兒時期，兒童時期，以及成人期。不同型之臨床表現與其鹼性磷酸酶之基因缺失有關。我們報告了兩位不同型之先天性磷酸酶缺乏症，分別是嬰兒型以及成人型。嬰兒型的病人其臨床表現為四個月大時出現發育不良，肌肉張力低，以及影像學上有佝僂症之表現。成人型之病人診斷時為十七八歲，臨床之表現為反覆性骨折以及影像學上出現骨質疏鬆之情形。兩個病人之血中鹼性磷酸酶皆呈現極低之數值。這兩例是台灣首度發表於文獻報告中之先天性磷酸酶缺乏症病例。

關鍵詞：先天性磷酸酶缺乏症，鹼性磷酸酶
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