

Original Article

Treatment of Hypophosphatemic Rickets with Phosphate and Active Vitamin D in Japan: A Questionnaire-based Survey

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Abstract. Hereditary hypophosphatemic rickets represented by X-linked hypophosphatemic rickets (XLH) is a rare disorder characterized by hypophosphatemia, elevated alkaline phosphatase (ALP) and undermineralization of bone. Active vitamin D and phosphate are administered to correct hypophosphatemia and elevation of ALP. Overtreatment with phosphate leads to secondary hyperparathyroidism, and a large dose of active vitamin D has a risk of hypercalciuria. To understand the situation concerning treatment of patients with hereditary hypophosphatemic rickets in Japan, we conducted a questionnaire survey of pediatric endocrinologists. Answers were obtained from 53 out of 68 hospitals where the pediatric endocrinologists worked. One hundred and thirty-five patients were treated in 28 hospitals during November 2009 and May 2010; 126 patients suffered from hereditary hypophosphatemic rickets, and 9 had hypophosphatemia caused by other miscellaneous reasons. The distribution of patient age was as follows: 27 (21%) were between 6 mo and 6 yr of age, 39 (31%) were between 6 and 12 yr of age, and 60 (48%) were more than 12 yr of age. Active vitamin D was given to 123 patients, and phosphate was given to 106 patients. As for the dose of phosphorus, 37.2–58.1 mg/kg/d was given divided into 2 to 6 aliquots. There were various control targets of treatment, including serum phosphate, serum ALP, rachitic change, urinary Ca/Cr, parathyroid hormone and growth. It is very important to avoid side effects of these treatments. No evidence is available about the optimal dose of phosphate or number of administrations in the treatment of patients with hypophosphatemic rickets. Although there is a recommendation for clinical management of patients with hypophosphatemic rickets, we should set a clinical guideline for it in Japan.

Key words: hypophosphatemia, phosphaturia, rickets, active vitamin D, phosphate

Received: June 22, 2012

Accepted: October 22, 2012

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Introduction

Rickets is a disorder of calcification in chondrocytes and bone characterized by accumulation of unmineralized bone, termed osteoid. Characteristic X-ray findings such as cupping, flaring, and fraying strongly suggest

rickets, although metaphyseal dysplasia must be ruled out. The main causes of rickets are vitamin D deficiency and hereditary hypophosphatemic rickets. Hypophosphatemia and elevated levels of alkaline phosphatase (ALP) are associated with both vitamin D-deficient and hereditary hypophosphatemic rickets.

Hereditary hypophosphatemic rickets is classified mainly into 4 entities based on mode of inheritance and urinary excretion of calcium (1, 2). Recently, the genes responsible for these forms of hereditary hypophosphatemic rickets have been identified. Autosomal dominant hypophosphatemic rickets (ADHR, MIM 193100) is a rare disease characterized by low levels of serum phosphate and elevated levels of ALP and phosphaturia and is inherited in an autosomal dominant fashion. In 2000, genetic analysis of families with the disease successfully identified that the *FGF23* (fibroblast growth factor 23) gene is responsible for the disease (3). Now FGF23 is recognized as a hormone that plays a central part in regulation of the serum phosphate concentration, and its abnormality is involved in many cases of hypophosphatemic rickets (4, 5). In ADHR, since the mutant FGF23 is resistant to degradation, its concentration is elevated in serum. Thus, this mutation is a gain-of-function type. FGF23 works as a phosphaturic factor after binding to FGFR1 and its co-receptor, klotho, in the kidney and reduces serum phosphate concentrations (6). In addition, FGF23 decreases the production of 1, 25-dihydroxyvitamin D [$1,25(\text{OH})_2\text{D}$] in renal tubules (7). In turn, $1,25(\text{OH})_2\text{D}$ and phosphate increase the expression of FGF23 (8). Therefore, administration of active vitamin D and phosphate may exert biphasic effects, i.e., acute increase in phosphate levels followed by decrease in phosphate levels associated with an increase in FGF23 levels.

Autosomal recessive hypophosphatemic rickets (ARHR1, MIM 241520) is also a rare disease in which hypophosphatemia and rickets are observed. The causal gene is *DMP1* (dentine matrix protein 1), and its expression is observed in

osteocytes and osteoblasts (9). *ENPP1* is a newly identified causal gene (ARHR2, MIM 613312) (10, 11). The *ENPP1* gene encodes ectonucleotide pyrophosphatase/phosphodiesterase 1 and is also responsible for generalized arterial calcification of infancy (12). Although the mechanism remains obscure, FGF23 is elevated in both types of ARHR and reduces serum phosphate concentrations (13). In Japan, two single families are reported to have abnormalities in each of these gene (14, 15).

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH, MIM 241530) is a rare autosomal recessive disease characterized by hypophosphatemia and hypercalciuria. It is caused by *SLC34A3*, which encodes the type IIc sodium-dependent phosphate co-transporter (NaPi-IIc), a transporter for reabsorption of phosphate in the proximal renal tubules (16–18). The administration of phosphate alone ameliorates hypophosphatemia and hypercalciuria in HHRH.

X-linked hypophosphatemic rickets (XLH, MIM 307800) is the most frequent and prototype form of hypophosphatemic rickets in pediatric practice. In 1995, the gene responsible for the disease was identified as *PHEX* (phosphate regulating gene with homologies to endopeptidases on the X chromosome) (19). To date, over 200 mutations have been found in the *PHEX* gene and listed in the PHEXdb, PHEX Locus Database (<http://www.phexdb.mcgill.ca>). Patients with XLH are treated with active vitamin D and phosphate buffer. However, phosphate buffer is not available as a prescribed medicine in Japan. In addition, treatment with vitamin D and phosphate buffer is not an absolute cure for the disease, though a recommendation for treatment has been published (20).

Hypophosphatemic rickets is also caused by impaired function of renal tubules and tumors that produce FGF23. Malfunction of renal tubules sometimes involves reabsorption of essential nutrients or minerals other than phosphate and is called Fanconi syndrome (MIM 134600, 613388, or acquired). The acquired form

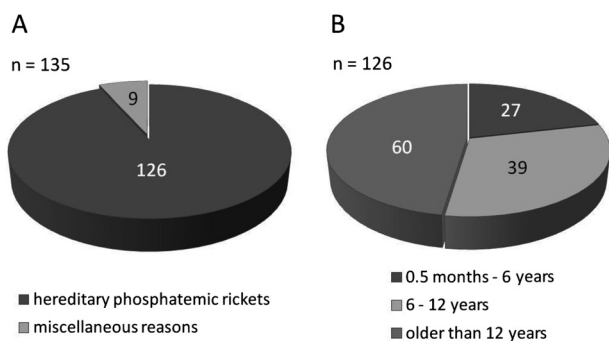


Fig. 1 Patient background. (A) The cause of hypophosphatemia in all patients. (B) The ages of the patients with hereditary hypophosphatemic rickets.

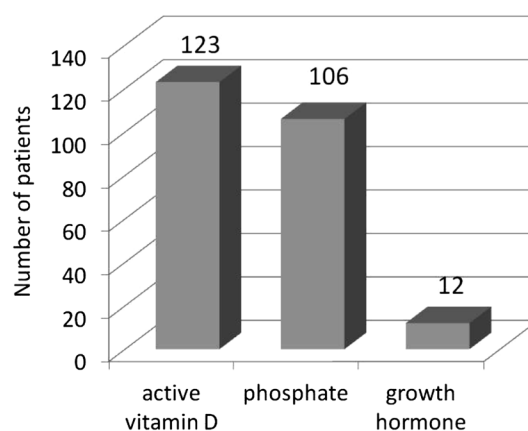


Fig. 2 Treatment for patients with hereditary hypophosphatemic rickets.

is called tumor-induced osteomalacia (TIO) and is rare in childhood (21–23).

We attempted to clarify how hypophosphatemic rickets is actually treated in Japan. To this end, we sent questionnaires concerning the experience of treatment of patients with hypophosphatemic rickets and the actual procedures.

Material and Methods

We sent questionnaires by mail to 68 hospitals where 80 pediatric endocrinologists approved by the Japanese Society of Pediatric Endocrinology worked in 2010. Survey subjects are patients who show hypophosphatemia for more than 6 mo. The questionnaire includes the number patients, patient profiles such as age and sex, hereditary pattern, type of medicine, and dose of phosphate including minimum and maximum dose and frequency.

Results

Responses to the questionnaire were obtained from 53 out of 68 (78% of total) hospitals to which the questionnaires were sent. A total of 135 patients were treated in 28 (53% of response) hospitals during November 2009 and May 2010; 126 patients suffered

from hereditary phosphatemic rickets, and 9 had hypophosphatemia caused by other miscellaneous reasons (Fig. 1-A). In this paper, we focused on the 126 patients who had hereditary hypophosphatemic rickets. Patient profiles were as follows: 27 (21%) patients were between 6 mo and 6 yr of age, 39 (31%) patients were between 6 and 12 yr of age, and 60 (48%) patients were more than 12 yr of age (Fig. 1-B). Active vitamin D and phosphate were administered to 123 and 106 patients, respectively. Twelve patients were treated with growth hormone (Fig. 2). The means of the minimum and maximum doses of phosphorus were 37.2 and 58.1 mg/kg/d, respectively, and the doses were administered in 2 to 6 aliquots (Table 1). Efficacy of the treatment was monitored by various factors including serum phosphate, ALP, intact PTH, urinary Ca/Cr, radiologic features, and growth. In particular, serum phosphate levels were monitored by 18 physicians. The target levels were set between 2 and 3.5 mg/dl. Serum ALP was also used as a marker by 17 physicians. The target levels varied from normal to 2,000 IU/l. In addition, 7 physicians employed intact PTH with target levels varying from normal to twice the normal level.

Table 1 Phosphorus dose and dose frequency

Dose (mg/kg/d)						
	Minimum dose			Maximum dose		
Mean	37.2			58.1		
Range	15–100			30–120		
Dose frequency						
Physicians that adjust dose frequency: 17						
	2 times/d	3 times/d	4 times/d	5 times/d	6 times/d	
Minimum	3	9	4	1	–	
Maximum	–	1	10	2	4	
Physicians that use a fixed frequency: 7						
	2 times/d	3 times/d	4 times/d	5 times/d	6 times/d	
	1	–	5	–	1	

Discussion

Hereditary hypophosphatemic rickets is often associated with bone deformity, bone pain and growth retardation. Bone deformity sometimes requires surgery for correction. At present, there is no curative therapy for XLH, and active vitamin D and phosphate are administered to correct hypophosphatemia and elevation of ALP (24). However, normalization of the serum phosphate concentration is difficult due to elevation of FGF23, leading to increased excretion of phosphate into urine (25, 26). Insufficient treatment is associated with growth retardation (27). On the other hand, overtreatment with phosphate leads to secondary hyperparathyroidism, and large doses of active vitamin D increase the risk of hypercalciuria (20). Though a recommendation for XLH treatment has been published, it is far from complete cure. Moreover, since phosphate is not a prescribed medicine in Japan, the buffer has to be prepared in the hospital dispensary.

To understand the situation concerning treatment of patients with hereditary hypophosphatemic rickets in Japan, we conducted a questionnaire survey among pediatric endocrinologists. The percentage of the

patients with XLH covered by this questionnaire is unclear, but in Japan, it is rare that pediatric nephrologists alone treat patients with XLH.

In the survey, 103 to 106 (82 to 84%) of 123 patients with hereditary hypophosphatemic rickets were treated with both active vitamin D and phosphate. At least 17 (13%) of the patients with hereditary hypophosphatemic rickets were treated with active vitamin D only. Twelve (10%) of the patients with hereditary hypophosphatemic rickets were treated with growth hormone, probably because they had short stature and growth hormone deficiency. The criteria for adjusting the dose of active vitamin D or phosphate buffer were various. One problem is that both serum phosphate and ALP values are age dependent, and normalization of serum phosphate levels and ALP was difficult. X-ray findings are not quantitative, and growth is long term. Thus, these indices are difficult to use in the short term. It is also critical to avoid side effects of the treatment. Thus, the doses of active vitamin D and phosphate should be reduced when hypercalciuria and secondary hyperparathyroidism are observed, respectively.

No information is available concerning the most effective dose of phosphate and how many times it should be administered in the treatment

of patients with hypophosphatemic rickets. In *Pediatric Endocrinology and Inborn Errors of Metabolism* (28), 40–100 mg/kg/d, divided into 4 to 6 doses, is recommended. However, adherence tends to become poor when short intervals are selected. In this survey, 37.2–58.1 mg/kg/d of phosphorus divided into 3 to 4 doses was most common. Thus, most physicians seemed to treat XLH patients within the recommended way of treatment in the actual clinical setting.

Acknowledgement

We are grateful to all the doctors who responded to the questionnaire.

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