Tertiary Hyperparathyroidism in X-linked Hypophosphatemic Rickets

Chung-Jung Wu, Yuh-Min Song* and Wayne Huey-Herng Sheu*

Abstract

We report a case of tertiary hyperparathyroidism in an X-linked familial hypophosphatemic rickets (XLH) patient under regular calcitriol and self-adjusted large doses of oral phosphate salt (2.4–3.6 g/day in 4–5 divided doses) according to his serum phosphate level. Tertiary hyperparathyroidism is an unusual complication of XLH patients during treatment. As there is growing evidence that a high phosphate diet may induce hyperplasia of the parathyroid glands, it is important to avoid the stimulation of the parathyroid glands by high doses of phosphate administration in XLH patients. Serum calcium, phosphate, alkaline phosphatase, and also parathyroid hormone should be measured regularly in order to facilitate an early diagnosis of secondary hyperparathyroidism during the treatment of XLH patients, since this stage is reversible with calcitriol and reduced doses of phosphate salt.

Key words: tertiary hyperparathyroidism, X-linked familial hypophosphatemic rickets, calcitriol, phosphate, hypercalcemia

Introduction

Secondary or tertiary hyperparathyroidism is often recognized in end-stage renal disease. However, chronic low serum ionized calcium levels seen in osteomalacia or rickets may stimulate parathyroid gland secretion and ultimately result in secondary or tertiary hyperparathyroidism. The exact prevalence and pathophysiology for the development of secondary or tertiary hyperparathyroidism in these patients is still unclear. Thus we report an X-linked familial hypophosphatemic rickets (XLH) patient with tertiary hyperparathyroidism, and note the early development of this complication under the combined therapy of vitamin D (calcitriol: 1,25-dihydroxycholecalciferol) and large doses of oral phosphate salt in XLH patients.

For editorial comment, see p 440.

Case Report

A 16-year-old male was brought to our clinic for evaluation of right shoulder pain. He was an XLH patient, which was diagnosed at 1.5 years old with the complaints of short stature, poor weight gain and characteristic roentgenographic findings as widening and flaying of metaphysis over both knee and ankle joints (Fig. 1). His cousin is also an XLH patient. After supplementation with vitamin D (calcitriol 0.5 microgram/day) and oral phosphate salt, his condition improved. His serum alkaline phosphatase level was normalized step by step, although there were frequent episodes of hypocalcemic twitching observed (see Fig. 2, first 4 years). Thereafter, only serum calcium, phosphate and alkaline phosphatase were checked by his physician. During his teenage years, although he did not have regular medical consultations, he use regular calcitriol and self-adjusted large doses of oral phosphate salt (2.4–3.6 g/day in 4–5 divided doses) according to his serum phosphate level. Since the age of 10–11 years, he occasionally felt general body aches with abnormal results of his blood biochemistry (low serum phosphate, mild hypercalcemia and elevated serum alkaline phosphatase levels). He did not pay much attention to this and just thought that the low serum phosphate and the elevated serum alkaline phosphatase levels were related to the disease process of XLH. Thus he had self-adjusted his medication to diminished calcitriol and elevated oral phosphate salt doses in the subsequent years without further medical consultation.

On examination, he had a short stature (146 cm), frontal bossing of the cranium, bulging of the costochondral junctions (rachitic rosary) and bowing of the lower limbs. A mildly tender right shoulder was found without evidence of fracture, but X-ray of fingers showed mild subperiosteal resorption and osteopenic change (Fig. 3). The serum level of intact PTH (para-
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thyroid hormone, analyzed by IMMULITE chemiluminescent immunometric assay, DPC, Los Angeles, USA) was 1,650 pg/ml (normal as 12–72 pg/ml), with simultaneous serum levels of calcium at 11.1 mg/dl (normal as 8.9–10.4 mg/dl) and phosphate at 2.5 mg/dl (normal as 3.0–4.6 mg/dl). The serum level of alkaline phosphatase was also very high at 2,795 IU/l. Other available parameters, such as serum creatinine, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, were all within normal limits during continuous oral phosphate salt and calcitriol usage (Table 1). Thus tertiary hyperparathyroidism associated with XLH was impressed after exclusion of renal insufficiency. The retrospective summary of serum calcium, phosphate and alkaline phosphatase since birth and concomitant medication regimen were plotted (Fig. 2).

Multiglandular parathyroid hyperplasia was found on sonography, but to date, his family has refused surgery.

Discussion

We report a case of tertiary hyperparathyroidism in an XLH patient who had been treated with calcitriol and relatively large doses of inorganic phosphorus for several years with resultant development of biochemical and radiographic evidence of hyperparathyroidism. XLH patients, which are characterized by hypophosphatemia, normocalcemia and rickets as growth failure and legs bowing, are usually treated with phosphate and vitamin D analogs. Before initiation of therapy, chronic hypophosphatemia may increase serum 1,25-dihydroxyvitamin D level via activation of renal 1 alpha-hydroxylase, leading to increased serum calcium and depressed PTH levels. Parathyroid function is usually described to be normal among these patients initially. With the treatment of XLH patients, there may be a diminished release of 1,25-dihydroxyvitamin D level with usage of calcitriol and oral phosphate salt (suppress renal 1 alpha-hydroxylase activity). These treatments may allow greater synthesis and secretion of PTH due to diminished 1,25-dihydroxyvitamin D. However, hyperparathyroidism is an unusual complication during the treatment of XLH patients (1).

Thus patients with XLH under the therapy of vitamin D and phosphate salt often have a depressed 1,25-dihydroxyvitamin D level, with a resultant increase in PTH values. This stage is termed secondary hyperparathyroidism, which is reversible. And this stage is often viewed as a compensatory response to either depressed 1,25-dihydroxyvitamin D level or relative hypocalcemia. However, it has been noted that depressed renal 1 alpha-hydroxylase activity due to intracellular phosphate retention is a major factor in the direct increase of parathyroid hormone (PTH) secretion in chronic renal insufficiency (2). Recently, Slatopolsky et al have shown that phosphorus, independent of serum calcium and calcitriol, increases PTH synthesis and secretion by a post-transcriptional mechanism, as a higher phosphate diet increases the PTH level and induces hyperplasia of the parathyroid glands (3, 4). So, in the presence of elevated PTH levels as seen in secondary hyperparathyroidism, high dose oral phosphate salts may further stimulate PTH secretion via multiglandular hyperplasia of the parathyroid glands in XLH patients. Finally, tertiary hyperparathyroidism develops; it is irreversible and functions as autonomous secretion of PTH.

These observations suggest that even with concomitant vitamin D (calcitriol) therapy, long-term oral phosphate supplementation may lead to the development of hypercalcemic hyperparathyroidism (5) or nephrocalcinosis (6). In tertiary hyperparathyroidism of XLH patients, the serum calcium level is usually normal or mildly elevated and the phosphate is low because of phosphate diuresis by PTH action, as seen in the present case. In autonomous tertiary hyperparathyroidism, it is theoretically necessary to perform parathyroidectomy.

The optimal treatment for XLH patients has not yet been established. However, combined therapy of oral phosphate salt and calcitriol is the best therapeutic approach at present. Vitamin D usage heals the bone lesions and phosphate salt supplementation contributes to better mineralization and improved growth velocity. But secondary or tertiary hyperparathyroidism is a potential complication during the treatment of XLH patients. More than three hundred XLH patients, complicated with secondary or tertiary hyperparathyroidism, have been reported with
Figure 2. Summary of laboratory results and medication dose. Mildly elevated serum phosphate level with relative hypocalcemia was present before age 10 under combined usage of vitamin D and phosphate salt. Since the age of 10, he has self-adjusted his phosphate dose to 2.4–3.6 g/day (as compared to previous doses of 1.6–2.4 g/day) with persistent mild hypercalcemia and a low phosphate level, that was due to the development of tertiary hyperparathyroidism. Serum PTH value was not monitored from age 4 to 16 (PTH value was 55.39 ng/ml at age 4).

ages ranging from 16 to 53 years old (7). The exact frequency of tertiary hyperparathyroidism in XLH patients is still unclear. However, there seems to be a higher incidence of the early development of hyperparathyroidism in XLH patients treated with vitamin D plus oral phosphate salt when compared with those treated with vitamin D only.

Hyperphosphatemia does not have any significant clinical effects except for occasional ectopic calcifications, depressed 1,25-dihydroxyvitamin D level (2) or even induced hyperplasia of the parathyroid glands (3, 4). Combined therapy of vitamin D and oral phosphate salt may further increase the intestinal absorption of phosphate in addition to calcium. Whether long-term therapy with vitamin D and oral phosphate salt will hasten the development of tertiary hyperparathyroidism in XLH patients is still unclear. Presently, to avoid the stimulation of the parathyroid glands by phosphate administration, serum calcium, phosphorus, alkaline phosphatase and even PTH should be measured regularly until the relationship of phosphate therapy and hyperparathyroidism in XLH patients is clearly elucidated. To prevent the occurrence of tertiary hyperparathyroidism in XLH patients, early diagnosis of secondary hyperparathyroidism is important. A lower dose supplement of phosphate salt during secondary hyperparathyroidism, a reversible state, is imperative for the success of calcitriol to con-
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Table 1. Serum Laboratory Results of This Patient at Diagnosis of Tertiary Hyperparathyroidism

<table>
<thead>
<tr>
<th>Variables</th>
<th>Results</th>
<th>(Normal range)</th>
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<tbody>
<tr>
<td>PTH (parathyroid hormone)</td>
<td>1,650 pg/ml</td>
<td>(12–72)</td>
</tr>
<tr>
<td>Calcium</td>
<td>11.1 mg/dl</td>
<td>(8.9–10.4)</td>
</tr>
<tr>
<td>Phosphate</td>
<td>2.5 mg/dl</td>
<td>(3.0–4.6)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>2,795 IU/l</td>
<td>(60–220)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.7 mg/dl</td>
<td>(0.5–1.4)</td>
</tr>
<tr>
<td>25-Hydroxyvitamin-D</td>
<td>17.93 ng/ml</td>
<td>(15–30)</td>
</tr>
<tr>
<td>1,25-Dihydroxyvitamin-D</td>
<td>25.24 pg/ml</td>
<td>(15–40)</td>
</tr>
</tbody>
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trol the further increased PTH levels.

References