Osteomalacia, Severe Thoracic Deformities and Respiratory Failure in a Young Woman with Anorexia Nervosa

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Abstract

The recent trends in avoiding sunbathing and eating fewer fish products have resulted in a high prevalence of vitamin D deficiency in the general Japanese population. We herein report the case of a young woman with enduring anorexia nervosa (AN) who suffered from osteomalacia, thoracic deformities and respiratory failure. Her vitamin D deficiency had been overlooked for years. Although the serum 25-hydroxyvitamin D [25(OH)D] level is a marker of vitamin D stores, it is not routinely examined because the cost is not covered by the national health insurance program. However, measuring the serum 25(OH)D levels in AN patients with hypocalcemia is recommended to prevent osteomalacia and osteoporosis.

Key words: anorexia nervosa, osteomalacia, respiratory failure, thoracic deformity, vitamin D deficiency

Introduction

The nutritional supplementation of vitamin D is not required in humans because this hormone is synthesized in the skin in response to ultraviolet light. The duration of exposure required to synthesize an adequate amount of vitamin D in Japanese adults living in Tsukuba near to Tokyo is less than 10 minutes at noon on a fine day in most seasons, except for winter (1). As the amount of vitamin D synthesized depends on the location, season, time and weather, significantly more time is required in the morning and afternoon to obtain the proper amount of vitamin D, in both summer and winter, than that at noon. The recent trend in avoid sunbathing without sunscreen to protect against ultraviolet irradiation has resulted in a high prevalence of hypovitaminosis D in winter (2). The alternative source of vitamin D is the diet. Major dietary sources of vitamin D include fish and fortified daily products. The habit of eating fewer fish products in Japan due to Westernization of the diet has also been reported to account for the increase in the prevalence of vitamin D insufficiency and deficiency in the general Japanese population (3-5).

Anorexia nervosa (AN) is characterized by self-induced weight loss as a result of inadequate food intake as well as estrogen deficiency. Osteoporosis is one of the most severe and common complications of AN (6). Whereas osteoporosis is defined as a decreased bone mass caused by increased bone resorption and/or inadequate bone formation, osteomalacia results from incomplete mineralization of cartilage due to metabolic defects in the vitamin D hormone system following closure of the epiphyses.

We herein report the case of a young woman with enduring AN who developed vitamin D deficiency, osteomalacia, severe spinal and thoracic deformities and respiratory failure requiring home oxygen therapy.

Case Report

A 21-year-old Japanese woman from Tokyo was admitted to our hospital due to generalized bone pain persisting for the last 28 months as well as a gait disturbance and respiratory distress that impaired her ability to complete activities of daily living in January, year X.

The patient had begun to lose weight at 12 years of age, with a height of 153 cm and body weight of 36 kg. She was amenorrheic and received estrogen replacement therapy; however, she discontinued the treatment herself due to ab-
dominal pain. She met the criteria for AN, as described in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (7) as well as those issued by the Survey Committee for Eating Disorders of the Japanese Ministry of Health, Labour and Welfare (6). After her first admission to a pediatric hospital in year X-8, the patient’s body weight increased from 28 to 34 kg with nutritional therapy, at which time her serum calcium level was 9.4 mg/dL. However, she stopped receiving regular medical intervention and treatment for AN in the spring of year X-3, when her serum calcium level was 7.7 mg/dL. As she had refused consultation for the past two years, clinical laboratory tests were not performed during this period. Her parents were unable to compel her to undergo a medical examination. The patient’s neck subsequently began to fall while walking, and she could not hold her head up while sitting. In December year X-1, she was no longer able to walk due to generalized pain and dyspnea and finally consulted our department. The patient had no family history of notable illnesses, including metabolic bone disease or AN, and she neither smoked nor drank alcohol. The type and amount of food she consumed had gradually decreased since approximately 15 years of age. Her last meal before admission had included only fruit, vegetables and brown rice, all of which contain very little or no vitamin D. She did not take any medications or supplements.

On admission, the patient was unable to stand without help due to pain in the lower limbs. She was emaciated, weighing 24 kg, and measured 120 cm in height due to the bending in her neck and remarkable dorsal hyperkyphosis. Her pulse was 103 beats per minute, her blood pressure was 97/72 mmHg, her respiratory rate was 30 breaths per minute and her body temperature was 36.5°C. Neither Chvostek’s nor Trousseau’s signs, both of which indicate hypocalcemia, were observed. She exhibited general skeletal tenderness and muscle weakness but no neurological abnormalities.

The results of the laboratory examination performed on admission are shown in Tables 1 and 2. Routine laboratory
studies revealed increased serum levels of aspartate aminotransferase, alanine aminotransferase, creatine kinase, amyrase and plasma growth hormone in addition to hypoglycemia, hypogonadism and a decreased serum concentration of insulin-like growth factor-1 (IGF-1), all of which were compatible with a diagnosis of AN. Meanwhile, the serum triiodothyronine level was decreased, while the thyroid stimulating hormone and free thyroxine levels were within the normal ranges, findings indicative of non-thyroidal illness. The white blood cell count, platelet count and hemoglobin, total protein, serum albumin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride and serum electrolyte levels were within the normal ranges, whereas the blood urea nitrogen and creatinine levels were below the normal lower limits. The most remarkable finding was severe hypocalcemia with normal levels of phosphorus and magnesium. The urinary excretion of calcium and phosphorus was also decreased. The serum 25-

| Table 1. Laboratory Findings on Admission |
|------------------------------------------|
| Urinalysis: occult blood (+), protein (+), sugar (+) |
| Complete blood cell count |
| WBC 4,810/μL |
| Hb 14.2 g/dL |
| Plt 31.6×10^4/μL |
| Blood chemistry |
| TP 7.2 g/dL |
| Alb 4.5 g/dL |
| AST 70 IU/L |
| ALT 43 IU/L |
| LDH 439 IU/L |
| ALP 1,517 IU/L |
| γ-GTP 23 IU/L |
| CK 496 U/L |
| Amy 225 U/L |
| HDL-cho 48 mg/dL |
| LDL-cho 118 mg/dL |
| TG 131 mg/dL |
| BUN 4.8 mg/dL |
| Arterial blood gas (room air) |
| pH 7.373 |
| PO2 49.2 mmHg |
| PCO2 54.8 mmHg |
| HCO3^- 31.2 mEq/L |
| PG: plasma glucose, ANA: anti-nuclear antibody |

| Table 2. Endocrinological and Special Examinations on Admission |
|------------------------------------------|
| intACT-PTH 478 pg/mL (Normal value 16-65) |
| estradiol 16.0 pg/mL (24.5-59.5) |
| progestosterone 0.40 ng/mL (0.2-1.5) |
| FT3 0.75 ng/mL (0.76-1.50) |
| FT4 1.09 ng/dL (0.94-1.60) |
| TSH 2.05 mU/mL (0.38-4.30) |
| GH 9.54 ng/mL (0.66-3.68) |
| IGF-1 66 ng/mL (168-459) |
| 1,25(OH)2D 5.2 pg/mL (20-60) |
| 25(OH)D ~5 mg/mL (30-60) |
| BALP 150 μg/L (7.0-10.0) |
| TRACP-5b 1,920 μU/mL (120-420) |
| FGF23 ~3 pg/mL (10-50) |
| Urinary Ca 0.02 g/day (0.1-0.3) |
| Urinary P 0.14 g/day (0.5-1.0) |
| TmP/GFR 2.95 |
| u-NTx 439.4 nMBCE/mM Cre (17.0-37.0) |
| Generalized aminoaciduria negative (negative) |
| iPTH: intact parathyroid hormone, FT3: free triiodothyronine, FT4: free thyroxine, TSH: thyroid stimulating hormone, IGF-1: insulin-like growth factor-1, 1,25(OH)2D: 1,25-dihydroxyvitamin D, 25(OH)D: 25-hydroxyvitamin D, BALP: bone-type ALP, TRACP-5b: tartrate-resistant acid phosphatase form 5b, FGF23: fibroblast growth factor 23, NTx: type I collagen cross-linked N-telopeptide |

A chest roentgenogram and computed tomography (CT) scan (Fig. 1C) revealed a severe deformity of the thorax and abnormal interstitial findings in both lungs. A blood gas analysis disclosed hypoxemia and hypercapnia (Table 1), thought to be caused by the thoracic deformity and aspiration pneumonia. Three-dimensional CT reconstruction images of the whole skeleton showed multiple vertebral fractures, marked thoracic kyphosis, scoliosis and severe deformities of the thorax, including the clavicles, sternum and ribs (Fig. 1D, E). The width of the cortex of the long bones was thin; however, no typical Looser’s zones or pseudofractures were observed. Radiographs of the bones showed generalized osteopenia. The bone mineral density and T-score of the total hip bones on dual X-ray absorptiometry were 0.176 g/cm^2 and -6.2, respectively; these values are only 20% of the young adult mean.

Although we did not perform a bone biopsy or skeletal scintigraphy, the patient was diagnosed as having osteomalacia based on the presence of typical symptoms as well as the laboratory findings indicating vitamin D deficiency, hypocalcemia, hypocalciuria, increased BALP and secondary hyperparathyroidism. The osteomalacia had induced severe spinal and thoracic deformities accompanied by type 2 respiratory failure.

The patient began treatment with alfacalcidol and calcium lactate, with a starting dose of 0.5 μg and 2 g per day, respectively (Fig. 2); these doses were gradually increased to 1.5 μg and 4 g per day, respectively. Eight weeks after the start of treatment, the serum calcium level increased from 5.6 to 9.0 mg/dL, the BALP and urinary excretion of NTx values decreased and her bone pain declined. Following the administration of intravenous hyperalimentation therapy, her body weight increased from 24 to 26.8 kg over six weeks, which subsequently improved the serum IGF-1 level, a useful nutritional marker, from 66 to 137 ng/mL. She was also
started on non-invasive positive-pressure ventilation with low flow rate of 0.25 L/min oxygen to prevent CO2 retention, which improved the arterial gas parameters. Eight weeks after admission, the patient was able to ambulate without assistance. After increasing her intake of calories, dairy products and vitamin D-rich foods, she gained more than 8 kg. However, the spinal and thoracic deformities remained, and she required home oxygen therapy for one year after discharge. The bone mineral density of the total hip ultimately increased to 61% of the young adult mean, and the dose of alfacalcidol was reduced from 1.0 to 0.5 μg a day because the serum calcium level had reached 9.9 mg/dL. She planned to undergo surgical treatment for dorsal hyperkyphosis but refused psychotherapy for AN.

**Discussion**

We herein reported the case of a young woman with long-term AN complicated by vitamin D deficiency-induced osteomalacia accompanied by spinal and thoracic deformities and severe respiratory failure that required home oxygen therapy.

Osteomalacia is caused by vitamin D deficiency and/or the decreased reabsorption of phosphorus (8). Nutritional and gastrointestinal disorders, 1α-hydroxylase impairment due to Fanconi syndrome or proximal-type renal tubular acidosis and hereditary resistance to vitamin D may also induce osteomalacia (9), as can familial X-linked hypophosphatemia or phosphatonin-producing mesenchymal tumors (tumor-induced osteomalacia) (10). In the current case, an undetectable serum level of 25(OH)D and low serum level of 1,25(OH)2D indicated severe vitamin D deficiency, which subsequently led to hypocalcemia and an increased serum level of iPTH. Because neither metabolic acidosis nor aminoaciduria were observed, the differential diagnoses of Fanconi syndrome and proximal-type renal tubular acidosis were excluded. The possibility of tumor-induced osteomalacia was also ruled out based on the low level of FGF23 and whole-body CT scan findings, which did not reveal any evidence of neoplasms. Furthermore, the lack of hypophosphatemia and suppressed serum level of FGF23 were not compatible with familial X-linked hypophosphatemia.

The predominant source of vitamin D is ultraviolet-dependent synthesis in the skin, rather than food-derived vitamin D. The causes of vitamin D deficiency in the present case are suspected to primarily include a lack of sunlight exposure due to lifestyle habits in which the patient spent most of the day indoors and the low or no vitamin D intake from meals associated with abnormal eating behaviors.

The clinical findings of osteomalacia in adults vary widely (11) and may include bowing of the legs, bone pain and muscle weakness, the latter two of which were observed in the present case. However, the patient’s family physician diagnosed her with fibromyalgia. Because the detection of hypophosphatemia or hypocalemia and/or elevation of the serum BALP level is essential for diagnosing osteomalacia (12), it is necessary for patients with enduring AN to undergo regular blood examinations to monitor the serum cal-
higher levels of serum phosphorus, suggesting that the ab-

sence of pseudofractures and/or vertebral fractures (15, 16). Although many AN patients exhibit vitamin D deficiency, cases of osteomalacia-associated AN are rare. We hypothesize that such cases, including the present case, share common predictors, such as long-standing AN, severe emaciation, osteoporosis and the lack of regular medical intervention or treatment. A 60-year-old woman showed the gradual development of severe thoracic deformities over a three-year period due to osteomalacia and respiratory failure, as in the present case; that patient had a history of AN in late childhood as well as ovarian resection (17). The causes of the thoracic deformities and serious kyphoscoliosis observed in the current case, particularly in the upper thoracic spine, are likely due to the effects of long-standing severe AN-induced osteoporosis, vitamin D deficiency, a delay in diagnosis and medical treatment and the patient’s history of sitting for long periods after leaving her job. In addition, the muscle weakness in the patient’s neck due to AN caused her to be unable to hold up her head while sitting, which exacerbated the spinal deformity. Furthermore, the pathological changes in the lung fields in this case were suspected to be due to aspiration pneumonia as a result of the thoracic deformity. Medication with alfacalcidol and calcium subsequently normalized the patient’s hypocalcemia, relieved her generalized bone pain and improved her ability to perform activities of daily living. However, the spinal and thoracic deformities remained, and the continued respiratory failure required treatment with home oxygen therapy. Therefore, we were unable to determine whether the main cause of the hypoxemia was the thoracic deformity. Although vitamin D and calcium supplementation inhibits the progression of deformities caused by osteomalacia, spinal surgery using spinal instrumentation is occasionally performed in such cases and has been shown to improve the symptoms of severe kyphoscoliosis and dyspnea (18). Hence, surgical treatment may provide some relief for the present patient.

In the United States, more girls with AN receive vitamin D supplementation than healthy controls, and the prevalence of vitamin D deficiency is thus lower among adolescents with AN than in healthy subjects in that country (19). However, in Japan, the general population, as well as patients with AN, exhibits a high prevalence of vitamin D insufficiency. A serum level of 25(OH)D <30 ng/mL and <20 ng/mL indicates vitamin D insufficiency and deficiency, respectively. In our institution, the serum 25(OH)D levels are lower than 20 ng/mL in 71% of patients with AN (unpublished data). Measurements of the serum calcium and phosphate levels are the main parameter used to detect vitamin D deficiency. However, the present patient discontinued consultation and did not undergo blood biochemical examinations for two years. Refusal of consultation and/or the interruption of treatment are common characteristics of difficult patients with AN, as described in previous reports (15, 16). The prevalence of AN among senior high school girls is approximately 0.26% according to a recent epidemiologic study (20), in which one-third of the patients with diagnosed or strongly suspected AN did not consult a physician. Unfortunately, the current patient’s family physician did not measure her serum calcium or phosphorus levels when she complained of generalized pain, and her parents were unable to compel her to undergo further examinations. Therefore, physicians should measure the serum calcium and phosphorus levels regularly in patients with possible metabolic bone disease, such as in cases of AN. Furthermore, measuring the serum 25(OH)D level is recommended in Japanese patients with AN who report reduced sun exposure and present with hypocalcemia in order to prevent osteomalacia and osteoporosis. Moreover, assessing the 25(OH)D level may be useful for making the differential diagnosis of vitamin D deficiency and determining the degree of vitamin D dependency. However, in Japan, the serum 25(OH)D level is not routinely measured because the test is not covered by the national health insurance program. Therefore, cases of vitamin D deficiency are often overlooked (21).

In conclusion, we herein reported the case of a young woman with enduring AN complicated by osteomalacia that induced the development of severe spinal and thoracic deformities and respiratory failure. Japanese patients with AN should be recognized as having a high risk for vitamin D deficiency in addition to osteomalacia and osteoporosis.

The authors state that they have no Conflict of Interest (COI).

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