

Unrecognized Severe Vitamin D Deficiency with Osteomalacia and Secondary Hyperparathyroidism: A Case Report

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Abstract

A 74-year-old woman presented with long-term intermittent arthralgia of the bilateral knee and ankle joints for the past year. The physical examination revealed a waddling gait and Gower's sign. Laboratory tests revealed a significant elevation of parathyroid hormone without hypercalcemia or obvious parathyroid lesions, which indicated secondary hyperparathyroidism. A serum 25-hydroxy vitamin D level of 2.34 ng/ml led to a diagnosis of severe vitamin D deficiency, which was the underlying cause of secondary hyperparathyroidism. The salt and pepper sign was also noted in calvarium radiography, but no significant subperiosteal reabsorption was observed in the long bones. The clinical manifestation, laboratory results, and radiographic findings further provided evidence for a diagnosis of osteomalacia. After receiving treatment with calcium infusions and vitamin D supplements, the symptoms were drastically improved. This report implies that clinicians should be more aware of the heterogeneous and potentially dangerous presentations of severe vitamin D deficiency. (J Intern Med Taiwan 2016; 27: 156-162)

Key Words: Osteomalacia, Secondary hyperparathyroidism, Vitamin D deficiency, Vegan

Introduction

Vitamin D is a group of fat-soluble vitamins that plays an important role in calcium and phosphate homeostasis. People normally produce vitamin D in the skin through sunlight exposure or acquire vitamin D from ingested food or dietary supplements. Very few foods in nature contain vitamin D, and cod liver oils are among the best dietary sources. Fish such as swordfish, salmon, tuna, and

mackerel also contain significant amounts, while other foods such as dairy cheese, beef liver, and egg yolks contain less vitamin D. None of these foods are eaten by people who stringently comply with a vegan diet.

An inadequacy of the production or intake of vitamin D may lead to different diseases depending on the age of the patient. In children, vitamin D deficiency causes rickets and delays the development of the skeletal framework, leading to a delay in

learning to walk. In adults, a deficiency can lead to osteomalacia, but the clinical signs are often subtle. Therefore, it is a considerable challenge to make a diagnosis in the early stages. Here, we report a case of osteomalacia with secondary hyperparathyroidism in a woman who is a strict vegan, presenting with intermittent arthralgia of the knee and ankle joints for over a year.

Case report

A 74-year-old woman had long-term intermittent arthralgia over the bilateral knee and ankle joints for about 1 year, and she was regularly followed up at the Geriatric outpatient clinic. About 2 weeks before admission, arthralgia occurred again in the right foot and then spread to the right knee and left foot. The pain at these three different sites presented with a similar pattern as before, with localized swelling and tenderness, which was at its worst in the early morning, but gradually improved during the day. The pain sometimes recurred in the afternoon and persisted during the night. The greatest magnitude of pain reported was a five on a scale of ten. The pain during the night occasionally interrupted her sleep; therefore, she would take an analgesic to relieve the pain. However, recently, the pain became more intense even after taking the medicine, causing the patient came to our outpatient clinic for medical attention.

The patient reported no history of gout or rheumatoid arthritis, but mentioned that she had osteoarthritis in the bilateral knee and ankle joints. On examination, there was localized tenderness, heat, and swelling at the bilateral ankle joints and the right knee. The distal pulses were bilaterally palpable. Due to this tenderness, the patient scarcely walked; her gait was a waddle but presented no drop foot. The joint movement of the bilateral ankles showed limited eversion. The patient also presented proximal muscle weakness at the bilateral lower limbs, therefore showing that she was positive for Gower's

sign. The patient's vital signs were stable without fever. The bilateral lung sounds were clear, and the heartbeat was regular without audible murmurs, rubs, or gallops. Her abdomen was soft, and there was no tenderness. The patient follows a strict vegetarian diet without egg or milk intake and seldom walks outdoors. There was no change in her bowel or voiding habits, and she did not have a significant decrease in her body weight over the past year. She did not report any upper respiratory symptoms such as a cough, rhinorrhea, or sputum production.

The complete cell count showed no leukocytosis, but macrocytic anemia was incidentally discovered. The serum vitamin B12 was less than 150 pg/ml. The total calcium level and phosphorus level were within the normal ranges. The serum parathyroid hormone (PTH) level was 666.8 pg/ml, which is above the upper normal limit. Parathyroid sonography revealed several nodules 0.2–0.8 cm in size located in both thyroid lobes, but no abnormal enlargement of the parathyroid gland was seen (Fig. 1). The serum 25-hydroxy vitamin D assay showed an extremely low level, at 2.34 ng/ml, and the serum alkaline phosphatase level was 291 IU/L. There were no abnormal findings in serum blood urea nitrogen (BUN), or creatinine levels. The 24-h urine analysis test showed a urine output of 1600 ml/day and decreased calcium excretion. The blood test and 24-h urine analysis results are shown in Table 1. An autoimmune survey showed an equivocal antinuclear antibody level with a titer of 1:160, and the extractable nuclear antigens level was 0.8 U/ml, while the rheumatoid factor was below the lower limit of 15.0 IU/ml. There was no decrease in C3 (103 mg/dl) or C4 (29.5 mg/dl) levels. The thyroid function test showed a normal level of thyroid-stimulating hormone, at 1.134 μ I U/ml, and free thyroxine (free T4) at 0.91 ng/dl (Table 1).

To assess skeletal integrity, the patient underwent radiography studies of the skull, hand, knee, foot, spine, and long bones. The calvarium was posi-

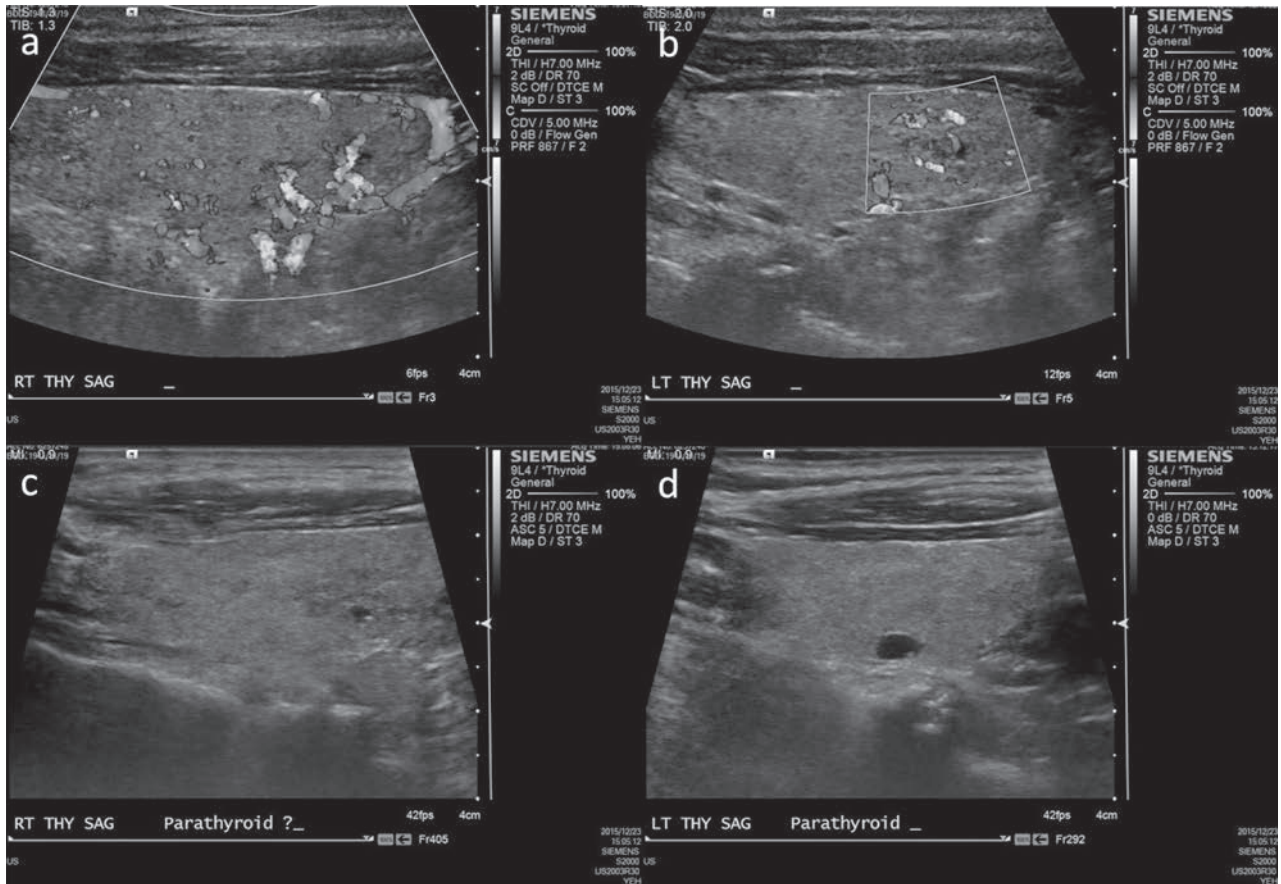


Figure 1. Parathyroid sonography revealed several nodules 0.2-0.8 cm in size located in both the right (a) and left (b) thyroid lobes, but no abnormal enlargement of the parathyroid gland was noted at either the right (c) or left (d) side.

tive for the salt and pepper sign, but the hand and long bone radiography scans showed no significant subperiosteal or intracortical resorption (Figure 2). Treatment for secondary hyperparathyroidism was initiated with a calcium gluconate infusion, after which the intact PTH (iPTH) levels decreased and returned to within the normal range, and the left ankle arthralgia improved dramatically. The series of iPTH levels is shown in Figure 3. Vitamin D and vitamin B 12 supplements were also given to treat the underlying vitamin D deficiency and macrocytic anemia. After two days of treatment, lower limb weakness and proximal muscle power improved significantly, and the patient was then discharged in a stable condition.

Discussion

Vitamin D deficiency is a common disease among the elderly, which has drawn an increasing amount of attention¹. It has been estimated that over 1 billion people worldwide have vitamin D deficiency². This deficiency reduces intestinal absorption of calcium and phosphorus, causing hypocalcemia and hypophosphatemia. PTH subsequently increases to compensate for the low level of calcium, leading to the development of secondary hyperparathyroidism, which further leads to demineralization of bones and osteomalacia in adults³. However, there is no current consensus on the optimal levels of 25-hydroxy vitamin D as

Table 1. Blood test and 24-h urine analysis at admission, and the iPTH level series after admission

Complete Blood Count	Concentration	Reference Range
White Blood Cell (WBC)	8000 /cumm	4000–10000 /cumm
Red Blood Cell (RBC)	3.27 M/cumm	4.2–5.4 M /cumm
Hemoglobin (Hgb)	11.0 g/dl	12–16 g/dl
Platelet (Plt)	224000 /cumm	150000–350000 /cumm
Mean Corpuscular Volume (MCV)	101.9 fl	80–96 fl
Serum Chemistry	Concentration	Reference Range
Sodium (Na)	138 mmol/l	135–147 mmol/l
Potassium (K)	4.0 mmol/l	3.4–4.7 mmol/l
Calcium (Ca)	8.5 mg/dl	8.4–10.6 mg/dl
Phosphate (P)	2.3 mg/dl	2.1–4.7 mg/dl
Magnesium (Mg)	2.7 mg/dl	1.7–2.9 mg/dl
Alkaline Phosphatase (ALP)	291 IU/l	13–100 IU/l
Albumin (ALB)	3.7 mg/dl	3.7–5.3 mg/dl
Creatinine (Crea)	0.65 mg/dl	0.5–1.2 mg/dl
Hormone	Concentration	Reference Range
Parathyroid Hormone (iPTH)	666.8 pg/ml	15–68.3 pg/ml
Thyroid-stimulating hormone (TSH)	1.134 mIU/ml	0.4–4.0 mIU/ml
Free Thyroxine (Free T4)	0.91 mg/dl	0.8–1.9 mg/dl
Vitamin	Concentration	Reference Range
25-hydroxyvitamin D	2.34 ng/ml	20–40 ng/ml
Vitamin B12	<150 pg/ml	187–883 pg/ml
Folate	8.7 ng/ml	3/1–20.5 ng/ml
24-h urine quantification tests	Total amount	Reference Range
Urine Output	1600 ml	
Sodium (Na)	179 mmol/day	40–220 mmol/day
Calcium (Ca)	40 mg/day	100–250 mg/day
Creatinine (Crea)	0.75 g/day	0.8–1.8 g/day
Phosphate (P)	0.4 g/day	0.4–1.3 g/day

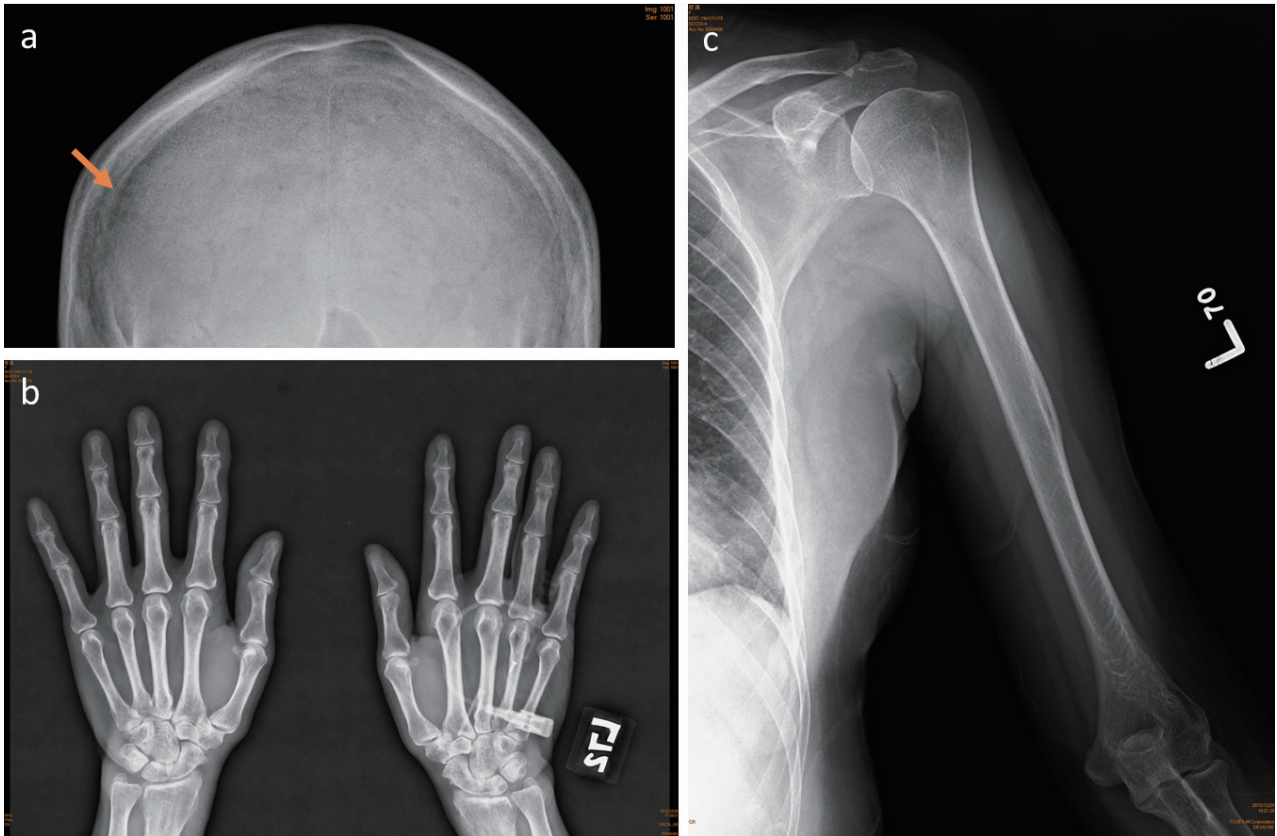


Figure 2. (a) The calvarium was positive for the salt and pepper sign. (b) No significant subperiosteal or intracortical resorption of the middle phalanges could be identified in the hand radiography. (c) The long bone radiography showed osteoporosis but an intact inner margin of the humeral cortex.

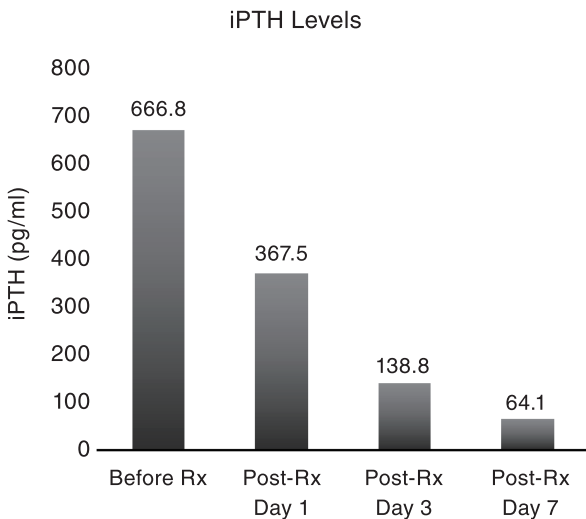


Figure 3. The level of iPTH significantly decreased after the treatment within the period of hospitalization. (Rx: Treatment of calcium infusion and vitamin D supplement).

measured in serum, but vitamin D insufficiency is commonly defined as a level less than 20 ng/ml⁴. Severe vitamin D deficiency is usually defined as a 25-hydroxy vitamin D less than 10 ng/ml.

The clinical manifestation of vitamin D deficiency varies among patients, and while most of cases with mild or moderate deficiency are asymptomatic, some may present with severe symptoms such as bone pain and muscle weakness^{2,5,6}. In osteomalacia patients, proximal muscle weakness with a waddling gait is a typical presentation. To make the diagnosis of osteomalacia, a comprehensive study of clinical manifestation, laboratory tests, and radiography findings is essential. The gold diagnostic standard is a bone biopsy, but this is rarely performed in current clinical practice due to its invasiveness. Non-invasive markers for the diagnosis of osteomalacia

include a decrease in serum 25-hydroxy vitamin D, calcium and phosphorus levels, raised iPTH levels, and a reduced excretion of urine calcium. The radiographic findings of osteomalacia varies depending on the causes and severity, and hyperparathyroidism associated with vitamin D deficiency may present radiographic signs, such as the salt and pepper sign in the calvarium, and subperiosteal or intracortical resorption of the phalanges. Some cases may also show cortical stress fractures, often called Looser zones or pseudofractures⁷.

In the present case, the waddling gait and positive Gower's sign were two clinical manifestations that suggested osteomalacia as a differential diagnosis; the laboratory results of borderline low calcium and phosphorus levels and elevated iPTH indicated secondary hyperparathyroidism, and the salt and pepper sign in the calvarium further supported the diagnosis of osteomalacia. The complaints of intermittent bilateral knee and ankle joint pain can be explained by the high turnover rate of bones under secondary hyperparathyroidism, leading to contiguous soft tissue swelling and inflammation. Although the underlying osteoarthritis can also display similar symptoms, the major difference between arthritis and vitamin D-related secondary hyperparathyroidism lies in the significant response to a calcium infusion. On the other hand, vitamin B12 deficiency in vegans has also been reported to cause bilateral limb pain as a major manifestation⁸, but peripheral neuropathy does not cause the intensive inflammatory response with swelling and tenderness, such as in this case.

An understanding of the etiology of vitamin D deficiency is crucial for planning the treatment strategy. The reduction in input of vitamin D from either cutaneous synthesis or dietary intake is the most common cause⁶. Other differential diagnoses include malabsorption derived from severe intestinal diseases, hepatic injury, end-stage renal disease, and intake of medication including anticonvulsants,

antirejection drugs, and glucocorticoids², but none of these were factors relevant to this case.

For vegans, the intake and plasma concentrations of 25-hydroxy vitamin D have been investigated in the EPIC-Oxford study. An analysis of 65,429 participants showed that vegans had the lowest mean intake of vitamin D and serum 25-hydroxy vitamin D level compared to meat eaters, fish eaters, and vegetarians⁹. However, the Adventist Health Study-2 in the US reported no significant difference in the serum concentration of 25-hydroxy vitamin D between meat eaters and vegetarians. The explanation relies on the similar total amount of vitamin D intake in either vegetarians or meat eaters, even though vegetarians did have a significantly lower intake of vitamin D if not count in supplements¹⁰. In Asia, a study in Vietnam also reported that around 75% of vegans had 25-hydroxy vitamin D levels below the normal limit¹¹, and a Korean study demonstrated that vitamin D deficiency and serum 25-hydroxy vitamin D level were associated with the consumption of vitamin D-rich food sources including fish and milk.¹² Therefore, some experts suggest that vegans should consume appropriate supplements if they do not regularly consume foods that are fortified with vitamin D^{9,11,13}. However, more studies are warranted on serum 25-hydroxyvitamin D levels in Taiwanese vegans.

This article illustrates a case of unrecognized severe vitamin D deficiency with osteomalacia and secondary hyperparathyroidism. This case shows that it is expedient to thoroughly collect lifestyle history information and assess the 25-hydroxy vitamin D level of those who adhere to a stringent vegan diet and have little sunlight exposure, particularly if they present with unexplained arthralgia and proximal muscle weakness. This report implies that clinicians should be aware of the heterogeneous and potentially dangerous presentations of severe vitamin D deficiency.

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嚴重維生素D缺乏表現軟骨病與次發性副甲狀腺亢進： 個案報告

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摘要

一位74歲女性，生活平時很少從事戶外活動，嚴格遵守純素飲食，近一年的求醫過程主訴雙側膝關節和踝關節間歇性疼痛，理學檢查發現步態蹣跚，高爾氏徵象(Gower's sign)呈陽性。進一步檢查顯示正常血鈣但副甲狀腺素升高，超音波無明顯副甲狀腺病變。血清25-羥基維生素D (25-hydroxyvitamin D) 濃度為2.34 ng/ml，符合嚴重維生素D缺乏症的診斷。典型的臨床表徵、血液檢查結果以及顱骨X光顯現黑白相間現象 (salt and pepper sign) 可作為骨軟化症診斷的依據。病患在住院期間接收鈣離子輸液和維生素D的補充後，症狀便有顯著改善。本篇個案報告強調要對嚴重維生素D缺乏保持相當的警覺心，因為臨床表現可以有相當大的差異性。