Vitamin D Deficiency - A Reversible Cause of Proximal Myopathy: A Case Report

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ABSTRACT

A 22-year-old married Hindu female, vegetarian, with lower socioeconomic status, presented with an insidious onset progressive bilateral lower limb symmetrical proximal muscle weakness without sensory and bladder and bowel involvement, from last 2 years. Bone scan reports were suggestive of mineral and bone disease. Vitamin D deficient osteomalacia was diagnosed based on elevated serum alkaline phosphatase levels, raised intact parathyroid hormone levels, decreased 25-hydroxyvitamin [25(OH)D] levels. Patient's symptoms improved after oral active vitamin D and calcium administration. The present case highlights the importance of considering vitamin D deficiency in patients presenting with musculoskeletal symptoms and a routine evaluation for vitamin D deficiency should be considered in all patients.

Keywords: Vitamin D deficiency, proximal myopathy, hypocalcemia, osteomalacia

Although the prevalence of vitamin D deficiency is common worldwide, it is often under-estimated. It is estimated that vitamin D deficiency or insufficiency affects around 1 billion population worldwide.[1] According to the previously published study reports, the prevalence of varying degrees of vitamin D deficiency with low dietary calcium intake in Indian population is extensive (50-90%).[2] However, the exact incidence of myopathy in individuals with hypovitaminosis D is unknown. Proximal myopathy has been reported to be present in 60-75% of patients with vitamin D deficiency.[1]

The weakness usually occurs in proximal muscles and it is often minimal and subclinical. Osteomalacia, by definition, means that osteoblasts have laid down a collagen matrix, but there is a defect in its ability to be mineralized. In children, a defect in the mineralization of the osteoid in the long bones and the failure or delay in the mineralization of endochondral new bone formation at the growth plate leads to the classic skeletal deformities of rickets. However, in adults, the mineralization defect takes on a different character due to the failure of mineralization of newly formed osteoid at sites of bone turnover of periosteal or endosteal apposition. Here, we present a case of severe muscle weakness with osteomalacia due to vitamin D deficiency, which rendered the patient wheel chair bound.

CASE REPORT

A 22-year-old female visited our outpatient clinic with weakness of bilateral lower limbs, which was gradually progressive from last 2 years. The patient, who was wheel chair bound from past 3 months, complained of bilateral lower limb pain, backache, severe fatigue and inability to walk without support and to get up from squatting position and slight difficulty in combing of hair and lifting of weight from last 3 months. There was no history of any trauma/steroid intake/periodic paralysis/chronic diarrhea/carpopedal spasm/hematuria/neck swelling/palpitations/tremors/jaundice/height loss/fragility fracture/antiepileptic intake/antitubercular intake. Patient had history of recent blood transfusions and was currently on oral iron and multivitamins supplements.

On examination, patient was conscious, well-oriented, had pallor with slight dark complexion. Her vitals were

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blood pressure (BP) - 120/80 mmHg, pulse - 84 bpm, respiratory rate (RR) - 16/min, body mass index (BMI) - 19.4 kg/m^2. She had regular bowels, bladder habits and sleep cycle. Her cardiovascular, respiratory and abdominal examinations were normal.

On central nervous system (CNS) examination revealed symmetrical proximal muscle weakness in bilateral lower limb with power of 3/5 at hip joint and in upper limb with power of 4/5 at shoulder joint and brisk deep tendon reflexes (DTR), and there was no sensory involvement. Skeletal examination revealed tenderness over lower back, hip and shin. Rest of the examination was normal.

Lab investigations revealed hemoglobin (Hb) - 10.4 g/dL, total leukocyte count (TLC) - 4,500, differential leukocyte count (DLC) - $P_{68}L_{28}M_2E_2$, platelet count - 4.2 lac. Kidney and liver function tests were normal. Patient had low serum calcium - 8.0 mg/dL, low serum phosphate - 1.8 mg/dL), raised serum alkaline phosphatase (ALP) - 874 IU/dL and serum albumin - 3.8 g/dL. Serum intact parathyroid hormone (PTH) level was 93.06 pg/mL (normal: 10-65 pg/mL) and serum 25-hydroxyvitamin D [25(OH)D] level was 18.68 nmol/L (normal: 75-100); immunoglobulin A anti-tissue transglutaminase antibodies (IgA-tTG) level was normal. The urine was negative for urinary albumin and glucose and pH was 6.0; 24-hour urinary calcium was 49.3 mg/day (100-300 mg/day). Antinuclear antibodies (ANA), thyroid function test and total creatine phosphokinase (CPK) level were normal. The bone mineral density (BMD) T-score and Z-score, as measured by dual-energy X-ray absorptiometry, was -2.7 and -2.5 at the lumbar spine and -2.8 and -2.0 at the femoral neck, respectively, indicating a low BMD for her chronological age.

Radiographic images revealed a pseudo-fracture in the right radial shaft and lower end of left femur (Fig. 1), bilateral superior pubic rami (Fig. 2), and first, second and fifth metatarsal bones along with diffuse osteopenia in B/L tarsals, metatarsals and phalanges (Fig. 3). Bone scan (technetium 99m-methyl diphosphonate [^{99m}Tc-MDP]) showed abnormal increased uptake by skull bone, scapula and upper limb bones, multiple ribs and vertebrae, pelvic bone, lower end of left femur and multiple metatarsal bones (Fig. 4). Electrophysiological study was suggestive of myopathy.

On the basis of examination and investigation, patient was diagnosed as a case of vitamin D deficiency with secondary hyperparathyroidism. The patient was treated with once weekly doses of cholecalciferol 60,000 IU along with calcium carbonate 500 mg twice-daily.

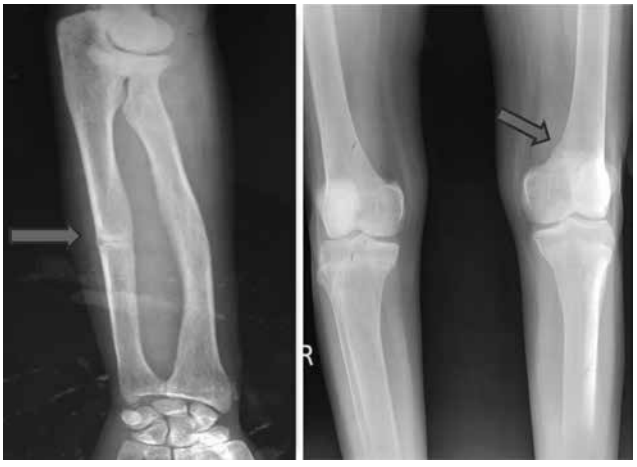

Figure 1. X-ray right forearm and lower end of left femur shows looser zone.

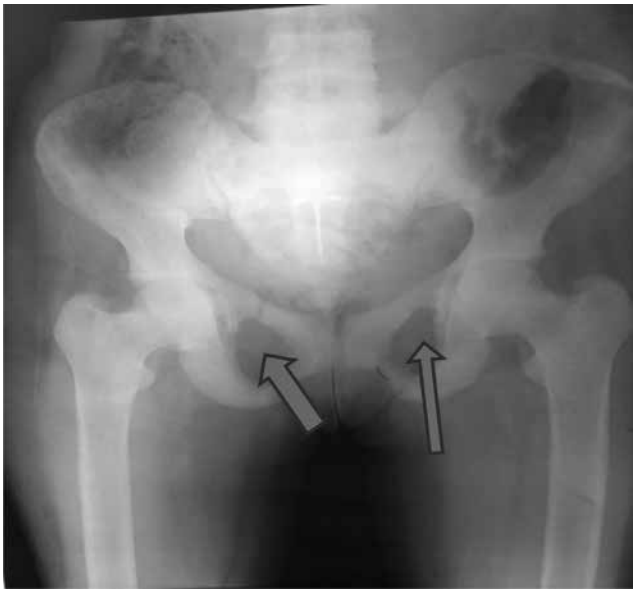

Figure 2. X-ray pelvis shows pseudo-fracture.

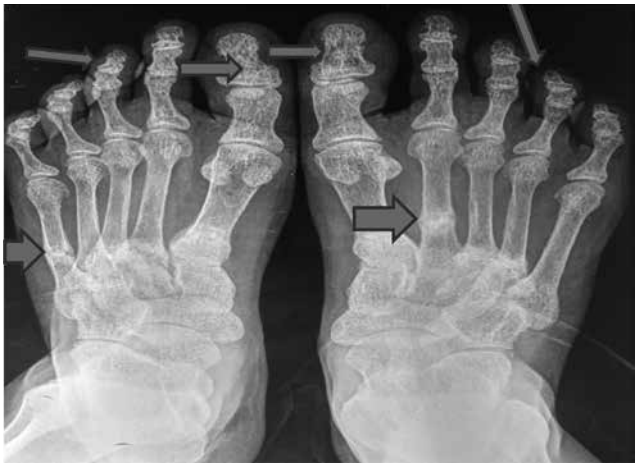

Figure 3. X-ray shows looser zone (*thick arrows*) and diffuse bone resorption (*thin arrows*).

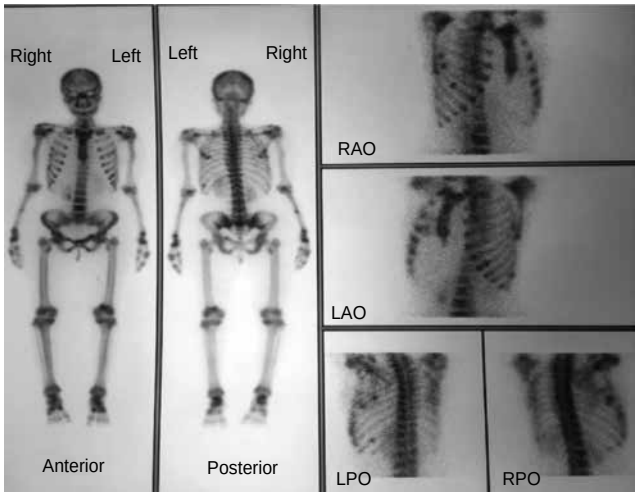

Figure 4. Bone scan.

Follow-up conducted at 4 weeks showed a gradual improvement in her symptoms. She was able to get up from chair and move without support and got significant relief in pain and fatigue. Levels of serum calcium and phosphorus were normalized but serum alkaline phosphatase (ALP) levels were still high (814 IU/L). At 3-month follow-up, pain, muscle weakness and gait disturbance had been completely alleviated and she resumed her routine daily activities. Biochemical parameters showed normal serum calcium, phosphorus as well as serum PTH and ALP. Patient is now on regular follow-up.

DISCUSSION

It has been estimated that over 1 billion people worldwide have vitamin D deficiency.[3] Vitamin D deficiency leads to decreased intestinal absorption of calcium and phosphorus, causing hypocalcemia and hypophosphatemia. Consequently, PTH secretion increases to overcome hypocalcemia which ultimately causes bone demineralization and osteomalacia in adults. In adults, osteomalacia usually does not present with any overt skeletal signs. However, patients with osteomalacia complain of throbbing, aching bone discomfort. Bone discomfort is worse when sitting or lying in bed. This is usually associated with proximal muscle weakness and aching in muscles.[4-6] Pressing on the skeleton resulting in discomfort is consistent with a trigger point that can lead to the misdiagnosis of fibromyalgia. In many cases, these patients are suffering from periosteal bone discomfort consistent with osteomalacia.

Several studies have shown an association between vitamin D deficiency and proximal myopathy. In most of the patients, muscle weakness, which is usually minimal, is revealed mostly on detailed history and physical examination. In infants, myopathy is evident from muscle weakness and hypotonia.[7] Adults may present with predominant proximal muscle weakness with difficulty in getting up from squatting position or climbing stairs. Other clinical characteristics of the disease include uniform generalized muscle wasting with preservation of sensation and DTR, and waddling gait.[8] Bone pain may also be present.

The case presented here had disabling muscle weakness and was not able to walk independently. Her serum calcium level was low-normal with low serum phosphorus with secondary hyperparathyroidism and elevated serum ALP. Normal serum levels of calcium and phosphorus in healthy individuals are achieved predominantly through interaction between the two hormones: PTH and calcitriol. In patients with vitamin D deficiency, secondary hyperparathyroidism causes release of calcium stored in bone and reabsorption of calcium by kidneys to maintain normal serum calcium till bony calcium is available. Hence, mild-to-moderate vitamin D deficiency is usually accompanied by normal blood levels of calcium, high-normal or elevated levels of PTH, elevated levels of ALP, a low 24-hour urine calcium excretion rate. Overt hypocalcemia and/or hypophosphatemia may appear only in patients with severe and long-standing vitamin D deficiency.[9]

However, the exact cause of the muscle weakness and bone discomfort is not fully understood, it is believed that because the major cause of osteomalacia is vitamin D deficiency and because skeletal muscle has a vitamin D receptor (VDR), the lack of 1,25-dihydroxyvitamin D [1,25(OH)2D] interacting with the skeletal muscle VDR increases muscle weakness.[10]

Metabolic myopathies may be often accompanied by secondary hypovitaminosis D. Biopsies can help in differentiating hypovitaminosis D myopathy (HDM) from other myopathies, but this is rarely performed in current clinical practice due to its invasiveness and better availability of noninvasive biochemical and radiological markers.

The mechanism of HDM remains controversial, and it is still not clear whether vitamin D deficiency itself or in association with secondary hyperparathyroidism is the primary cause of muscle tissue and functional abnormalities. PTH production, induced by low vitamin D levels, may confer direct effects on skeletal muscles.

It is important to evaluate vitamin D deficiency as a cause of myopathy in suspected cases. Severe vitamin D

deficiency is easily treatable. Generally, advocated strategy is to prescribe a loading dose (50,000 IU of oral vitamin D once a week for 2-3 months or three times weekly for 1 month). A previous analysis of multiple loading algorithms indicated that a minimum total dose of 6,00,000 IU best predicted an end-of-treatment 25(OH)D concentration >30 ng/mL. For mild-to-moderate deficiency (11-25 ng/mL), a shorter term treatment or lower dose may be effective. In cases with recurrent deficiency, maintenance daily dose of 800-2,000 IU or more will be required. Treatment using high-dose vitamin D for 6 months or more may be essential for full normalization of HDM.

The present case highlights the significance of considering treatable causes first in patients presenting with musculoskeletal symptoms. A routine test for hypovitaminosis D should be considered in patients with musculoskeletal symptoms such as bone pain, myalgia and generalized weakness; as there is an increased chance for misdiagnosing hypovitaminosis D-associated symptoms as fibromyalgia, chronic fatigue, age-related weakness or depression.

CONCLUSION

It is always worthwhile to look for common and treatable factors causing metabolic bone disease. HDM is a common cause for proximal muscle weakness and osteomalacia. Raised ALP and PTH levels should always be worked up to diagnose vitamin D deficiency, which is easily treatable. Myopathy linked to vitamin D deficiency is completely reversible.

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