Vitamin D Deficiency as an Ignored Cause of Hypocalcemia in Acute Illness: Report of 2 Cases and Review of Literature

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Abstract: We describe the clinical and laboratory findings in 2 cases of hypocalcemia secondary to vitamin D deficiency in intensive care unit and the response of calcium to treatment. We also discuss the mechanism and review pertinent literature. The first patient was admitted due to stroke. Laboratory data included serum calcium 7.6 mg/dl, intact parathyroid hormone (PTH) 891.6 pg/ml, 25-hydroxyvitamin D (25-OH-D) 7 ng/ml (17.5 nmol/l), 1,25-dihydroxyvitamin D (1,25-OH-D) 43 pg/ml (103.2 nmol/l), and corrected QT (QTc) interval 494 msec. After two weeks of treatment with oral calcium and ergocalciferol, serum calcium and intact PTH levels and QTc interval normalized. The second patient was transferred for the management of disseminated cytomegalovirus infection. Laboratory work-up revealed serum calcium 7.7 mg/dl, creatinine 4.3 mg/dl, intact PTH 207.5 pg/ml, 25-OH-D <5 ng/ml (<12.5 nmol/l), 1,25-OH-D <10 pg/ml (<24 nmol/l), and QTc interval 505 msec. After treatment for vitamin D deficiency and infection, we observed normalization of creatinine, corrected calcium, intact PTH and QTc interval. The clinical courses were uneventful in both cases. In conclusion, we would like to emphasize that vitamin D status should be evaluated in patients with hypocalcemia in acute settings because vitamin D deficiency is common and readily treatable, and there may be clear life-threatening consequences if it is not treated.

Keywords: Vitamin D, hypocalcemia, hyperparathyroidism, acute illness.

INTRODUCTION

Vitamin D deficiency is common in inpatients [1], outpatients [2], the elderly [3, 4], diabetic patients [5] and even in healthy adults [6-8]. It causes long-term sequelae including secondary hyperparathyroidism, bone loss, mineralization defects and fracture. Simple treatment with vitamin D and calcium has been shown to correct serum calcium and to reduce the fracture risk [9-12]. In addition, resulting hypocalcemia may lead to serious acute sequelae including neuromuscular irritability, tetany, laryngospasm [13], seizure, arrhythmia, heart failure [14], and death. Despite its high prevalence and important public health implications, vitamin D deficiency is frequently overlooked.

Hypocalcemia and consequent hyperparathyroidism are common in acute illness such as sepsis, acute pancreatitis, or major surgery, and they have been reported to predict mortality in these settings [15-22]. Although vitamin D deficiency is frequent and it has been described as a cause of hypocalcemia, it has received little attention and only few reports scrutinized vitamin D status and response in acute disease [23-26].

We describe 2 cases of severe vitamin D deficiency with persistent hypocalcemia and marked hyperparathyroidism during critical illness. After vitamin D treatment, we observed normalization of serum calcium, intact parathyroid hormone (PTH), and corrected QT (QTc) interval on electro cardiogram (ECG) in both cases. We would like to emphasize that presence of risk factors for vitamin D deficiency should raise alert about the need to test vitamin D status in patients with hypocalcemia in acute settings because vitamin D deficiency is common and readily treatable, and there may be clear morbid consequences if it is not treated.

CASE REPORTS

Case 1

A 67-year-old man with no past medical history was found in coma and admitted to the intensive care unit in winter. Soon after arrival, he developed cardiopulmonary failure and was intubated. Physical examination showed fixed constricted pupils, irregular heart beat, and slightly spastic lower extremities. Laboratory data included calcium 7.6 mg/dl (normal, 8.4-10.2 mg/dl), phosphorus 1.9 mg/dl (normal, 2.4-4.5 mg/dl), magnesium 1.7 mEq/l (normal, 1.4-1.8 mEq/l), albumin 4.0 g/dl (normal, 3.5-5.2 g/dl), thyroid stimulating hormone (TSH) 55 μIU/ml (normal, 0.4-4.5 μIU/ml), free thyroxine (FT_4) 0.5 ng/dl (normal, 0.76-1.79 ng/dl), and normal liver/renal functions. ECG showed atrial fibrillation and QTc interval 494 msec (normal, less than or equal to 440 msec). Initial head CT scan was negative.

He was diagnosed with stroke, atrial fibrillation, hypothyroidism, and hypocalcemia. Subsequently, he was given levothyroxine 50 μg daily and one dose of intravenous calcium gluconate 1000 mg (elementary calcium 90 mg) was

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1874-2165/09

given over 10 minutes. Brain MRI and repeat head CT 2-3 days after admission revealed marked brain stem infarction. He regained consciousness on hospital day 7 and he was extubated on day 10. Serum albumin stayed in the normal range throughout the course of hospitalization. Further work-up for hypocalcemia revealed serum hydroxyvitamin D (25-OH-D) 7 ng/ml (17.5 nmol/l; normal, 8-38 ng/ml [20-95 nmol/l]), 1,25-dihydroxyvitamin D (1,25-OH-D) 43 pg/ml (103.2 nmol/l; normal, 22-67 pg/ml [52.8-160.8 nmol/l]) both measured by radioimmunoassay, and intact PTH 892 pg/ml (normal, 14-72 pg/ml) measured by electrochemiluminescent immunoassay. Ionized calcium was not measured and an ultrasound evaluation of thyroid/parathyroid was not performed. On day 9, he was started on ergocalciferol 50,000 units daily for 2 weeks in conjunction with oral calcium (500 mg elemental) with vitamin D three times daily. Subsequently, serum calcium level rose to near-normal level (Fig. **1**) and intact PTH level declined to 378 pg/ml on day 10, 291 pg/ml on day 12, and 44 pg/ml on day 28. QTc interval shortened to 400 msec.

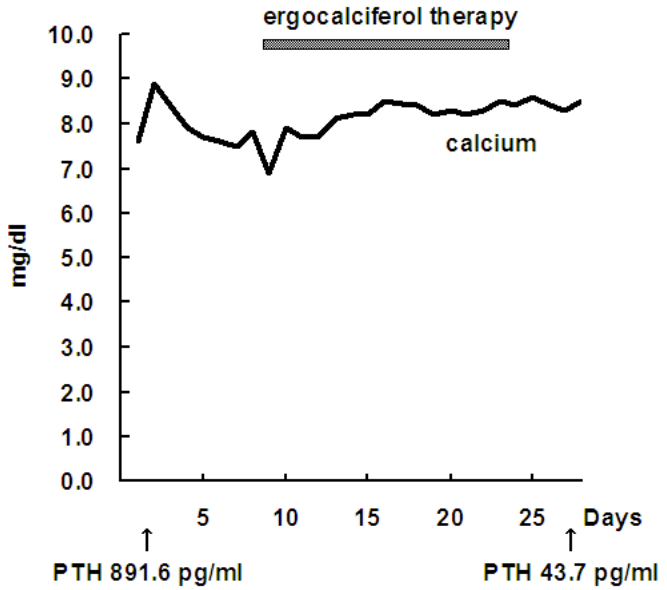

Fig. (1). Change in serum calcium concentration with time in Case 1. PTH = parathyroid hormone.

Case 2

A 50-year-old man was admitted to another hospital in winter because of acute onset respiratory failure for which he was intubated. He was found to have disseminated cytomegalovirus infection with acute renal failure, and he was transferred to our institution for intensive management one week later. His past medical history was significant for myasthenia gravis and hypothyroidism. The serum calcium level and the renal function one week prior to this event were normal. His medications on transfer included intravenous immunoglobulin, mycophenolate mofetil, levothyroxine, and intravenous ganciclovir. Laboratory data on transfer were as follows: creatinine 4.3 mg/dl, calcium 7.7 (albumin-adjusted 8.4) mg/dl, phosphorus 2.4 mg/dl, magnesium 1.8 mEq/l, albumin 3.1 g/dl, TSH 0.4 mIU/l, and FT_4 0.6 ng/dl. The other liver function test was normal. QTc interval on ECG was 505 msec.

Subsequently, he developed septic shock due to disseminated cytomegalovirus infection. Additional endocrinological work-up for persistent hypocalcemia showed ionized calcium 4.6 mg/dl (normal, 4.6-5.4 mg/dl), 25-OH-D <5 ng/ml (<12.5 nmol/l), 1,25-OH-D <10 pg/ml (<24 nmol/l), and intact PTH 207.5 pg/ml. On day 11, he was initiated on ergocalciferol 50,000 units daily for 2 weeks and oral calcium (500 mg elemental) with vitamin D three times daily. Serum creatinine level returned to normal on day 14. He regained consciousness on day 16 and he was extubated on day 19. Serum albumin remained in the range of 2.1-2.4 g/dl during the rest of hospitalization. Corrected calcium level returned to normal range (Fig. **2**) and intact PTH level decreased to 49.7 pg/ml on day 28. QTc interval shortened to 430 msec.

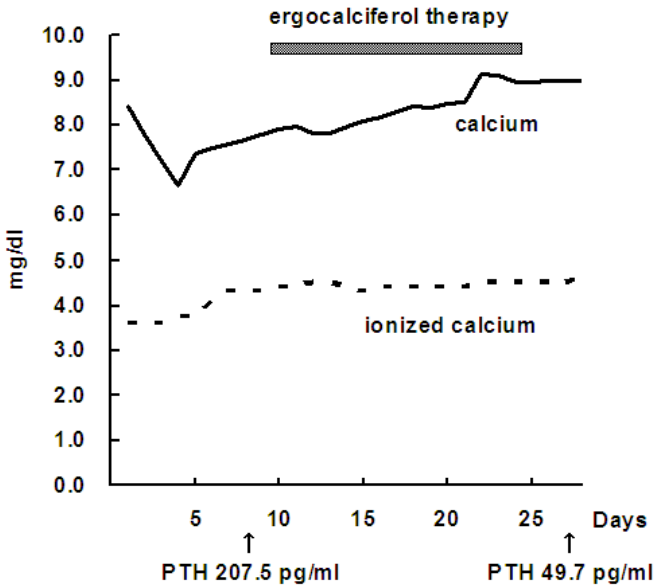

Fig. (2). Change in serum calcium concentration with time in Case 2. PTH = parathyroid hormone.

DISCUSSION

These two patients with critical illness had hypocalcemia and marked hyperparathyroidism secondary to vitamin D deficiency. Their responses to treatment with vitamin D support vitamin D deficiency as the most plausible cause of hypocalcemia. Moreover, the low serum phosphate levels in both cases were consistent with vitamin D deficiency-induced hyperparathyroidism since PTH induces phosphaturia and hypophosphatemia.

Hypocalcemia is frequent in the critically ill [15]. It can lead to serious conditions [13, 14]; it has been suggested that hypocalcemia is associated with the severity of disease and fairly predicts mortality in critically ill patients [15-17, 19]. Hypocalcemia in critical illness is presumably multifactorial. In addition to the common causes of hypocalcemia (Table **1**), other factors have been postulated [15, 16, 19, 21, 23, 26, 27]: failure of the kidney to produce 1,25-OH-D, failure of the liver to produce 25-OH-D, effects of cytokine, blunted response of the bone to PTH, relative hypoparathyroidism, and chelation by citrate in transfused blood. However, we speculate that vitamin D deficiency may be an important cause in light of its high prevalence and poor nutritional state

with lack of sunlight exposure in very sick patients [28] like our pateints, although very few studies have published low to low-normal vitamin D level in patients with acute diseases (Table **2**) [23-26].

Table 1. Causes of Hypocalcemia

Vitamin D deficiency (including treatment with phenytoin or phenobarbital) or resistance
Hypoparathyroidism or resistance (including magnesium deficiency)
Pseudohypocalcemia (Hypoalbuminemia)
Redistribution: Hyperphosphatemia (including rhabdomyolysis, tumor lysis syndrome), acute pancreatitis, post-transfusion, alkalosis, blastic bone metastases, hungry bone syndrome
Drug treatment: Bisphosphonates, phosphate, foscarnet, ketoconazole
Unclear cause: acute severe illness

The major risk factors of vitamin D deficiency are listed in Table **3**. Most mineral experts suggest that the lower limit of normal range should be > 20 ng/ml (50 nmo/l) [36] or even 30 ng/ml (75 nmol/l) [37, 38]. In Case 1, vitamin D deficiency was presumably attributable to little sunlight exposure and poor intake of vitamin D. In Case 2, long-standing poor dietary intake of vitamin D before transfer in addition to poor sunlight exposure probably accounted for the undetectable 25-OH-D level. Malnutrition is also suggested by hypoalbuminemia. In addition, it is also likely that 1,25-OH-D depletion resulted from superimposing acute renal failure and that sepsis and acute renal failure exacerbated hypocalcemia and secondary hyperparathyroidism. In both cases, liver function was intact and vitamin D resistance was unlikely because 1,25-OH-D was not high.

Table 2. Vitamin D Levels in Reported Cases with Acute Illness

	Diagnosis	Cases (n)	25-OH-D (ng/ml)	1,25-OH-D (pg/ml)
Lind, *et al*. 2000 [23]	sepsis	13	12.0 (5.6)	17.5 (8.8)
	surgery	13	13.6 (4.0)	17.9 (7.5)
Muller, *et al*. 2000 [24]	infection	48	8.8 (7.7)	32.4 (15.0)
	no infection	20	8.1 (6.1)	25.0 (13.1)
	sepsis	33	6.3 (5.2)	27.7 (23.5)
Zaloga, *et al*. 1987 [25]	sepsis	12	15.1 (8.0)	20.5 (23.6)
Desai, *et al*. 1987 [26]	normocalcemia	10	26.5 (17.0)	not measured
	hypocalcemia	28	15.3 (9.2)	not measured

Values of vitamin D are shown in means (SD).

PTH is one of the major regulators of extracellular calcium lying in a negative feedback way responding to changes in ionized calcium levels and vitamin D. PTH reportedly affects vascular smooth cells and ventricular myocytes [29], and impairs cardiac energy production, transfer, and utilization by enhanced entry and the accumulation of calcium in the myocardium [30] leading to development of cardiovascular disease [20, 31-33]. There have been several reports of elevated PTH value in patients with acute disease, which was associated with disease severity and poor outcome [17-20]. In most cases with acute illness, hypocalcemia was not restored by elevated concentration of PTH. This points to the possibility that secretion or action of PTH is relatively impaired in addition to vitamin D deficiency [15, 25, 34]. It is also conceivable that PTH might affect cytokine link [19, 27] and immune system [35], resulting in refractory hypocalcemia.

In Case 1, hypocalcemia had not been restored by high PTH and the initial PTH value was disproportionately elevated to the low 25-OH-D level [1, 3]. The PTH value was normalized in a short term as seen in previous reports in which a similar spontaneous decline of PTH concentration within 4-10 days was described [19, 21, 22]. The decrease in PTH by ergocalciferol supplementation should have been slower in a chronic vitamin D deficient state. These facts suggest possible PTH resistance in addition to vitamin D deficiency. However, the exact etiology remains elusive and it requires further investigations.

Table 3. Risk Factors of Acquired Deficiency or Resistance to Vitamin D

Poor intake / malnutrition
Malabsorption
Diarrhea
Poor sunlight exposure
Skin pigmentation
Liver disease
Renal disease
Hypomagnesemia
Older age
Anticonvulsant-drug therapy

Recent investigation has revealed vitamin D-binding protein (DBP), also known as Gc-globulin, is an acute phase reactant which falls in the event of acute disease. Dhal, *et al*. [39] reported that it decreased acutely to 87 % of baseline value following surgery, suggesting that acute situations potentially result in acutely low 25-OH-D even in a patient with reasonable body stores. Although 88% of 25-OH-D is bound to this protein in the serum [40], only 5% of the binding sites are normally occupied on the circulating DPB. Thus, an even higher decrement in DBP is required to significantly lower serum 25-OH-D [41]. Such reductions occur in only a few clinical conditions such was severe hepatic failure, nephrotic syndrome, and severe malnutrition [42, 43], and our cases were not compatible with these clinical conditions.

In conclusion, vtamin D deficiency is common but frequently overlooked. This is the first report to our knowledge that followed the serial values of serum calcium and PTH in response to vitamin D treatment in the setting of acute illness. It should be assessed as a cause of hypocalcemia because it is simply treatable as illustrated here. Our cases point up the fundamental fact that severe hypocalcemia constitutes an emergency that requires immediate attention and appropriate treatment to prevent life-threatening events.

ACKNOWLEDGMENT

We are grateful to Dr. M. Larissa Aviles-Santa for her clinical advice during the care of these patients.

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Received: October 21, 2008 Revised: January 13, 2009 Accepted: January 14, 2009