A case report of defective endogenous vitamin D: a new clinical entity

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Summary

Objective. To report a case of defective endogenous vitamin D with excellent response to low dose calcitriol replacement therapy.

Methods. We describe the patient’s clinical presentation, biochemical workup, and clinical course.

Results. The patient initially presented with severe symptomatic hypocalcemia and was diagnosed with pseudohypoparathyroidism type 1b at an outside hospital and started on calcitriol 2.25 mcg twice daily with good response but calcitriol was stopped later for cost concerns which led to recurrence of symptoms, worsening hypocalcemia and increased parathormone levels. On review of her case it was noted that her 1,25 dihydroxy: vitamin D level was within normal limits even before she started taking calcitriol, which is not consistent with pseudohypoparathyroidism type 1b. Restarting low dose calcitriol (0.25 mcg twice daily) improved the patient’s calcium level to 10.1 mg/dl and decreased the parathormone level to 17 pg/ml and symptoms resolved. Conditions associated with low serum calcium and high parathormone include pseudohypoparathyroidism, vitamin D deficiency and vitamin D resistance. This patient does not fit into any of the known entities causing hypocalcemia and elevated parathormone.

Conclusions. We hypothesize that this patient had an inadequate number of vitamin D receptors that was corrected by exogenous administration of vitamin D.

Case description

The patient was a 44 year old female with no significant past medical history who initially presented to an outside hospital with complaints of spontaneous muscle spasms and positional dizziness. Labs were remarkable for a serum calcium level of 6.5 mg/dl (8.6-10.6 mg/dl), serum phosphorous of 4.8 mg/dl (2.3-4.7 mg/dl), serum parathormone level of 129 pg/ml (15-65 pg/ml) and 24 hour urine calcium of 28 mg. A DEXA (Dual-energy X-ray absorptiometry) scan was performed which showed mild osteopenia with a T score of -1.2 at left hip and -0.9 at left femur neck. Urine cyclic AMP after PTH infusion was not measured. A diagnosis of pseudohypoparathyroidism (PHP) type 1b was made and the patient was started on calcitriol 0.25 mcg by mouth twice daily and calcium carbonate 500 mg oral once daily. Her symptoms resolved, calcium improved to 9.8 mg/dl and PTH level decreased to 33 pg/ml. 1.25 vitamin D level measured two different times while on calcitriol was 38 and 48 pg/ml (normal 15-75 pg/ml). Because of cost concerns, calcitriol was discontinued and the patient was started on oral vitamin D3 800 units daily and continued on calcium carbonate 500 mg oral once daily. With the change in therapy she again developed hypocalcaemia and secondary hyperparathyroidism (Figure 1) along with intermittent muscle spasms. During this period her vitamin D and calcium dose was gradually increased to 2000 units oral daily and 1000 mg oral daily respectively but she continued to be symptomatic and was referred to endocrinology. On review she denied any family history of hypocalcaemia or thyroid cancer. Exam was remarkable only for short stature (58 inches) and slightly bowed legs.

The initial differential diagnoses included pseudohypoparathyroidism type 1b or 2, vitamin D dependent rickets and vitamin D resistant rickets. Her lab values while taking 2000 units vitamin D and 1000 mg calcium carbonate were: calcium 8.6 mg/dl (8.6-10.6 mg/dl), 25 OH vitamin D level 59 ng/ml (30-80 ng/ml), 1.25 OH vitamin D level 44 pg/ml (15-75 pg/ml), parathormone 147 pg/ml (15-65 pg/ml), magnesium 2.4 mg/dl (1.6-2.6 mg/dl), phosphorous 3.4 mg/dl (2.4-4.1 mg/dl), Calcitriol 0.25 mcg twice daily was restarted and labs rechecked in 4 weeks demonstrated: calcium 10.1 mg/dl (8.6-10.6 mg/dl), 25-vitamin D 53 ng/ml (30-80 mg/ml) and PTH 20 pg/ml (15-65 pg/ml).

Introduction

Calcium homeostasis is tightly regulated by the interplay between vitamin D and parathormone (PTH) (1, 2). Deficiencies in either of these two hormones will cause hypocalcemia. In addition to deficient levels of PTH and vitamin D, hypocalcemia can be caused by mutations that up-regulate the calcium sensor (3), PTH resistance at the receptor level (4) (pseudohypoparathyroidism), defects in 1α-hydroxylation of vitamin D and vitamin D resistance (5). We report a patient with hypocalcemia who does not fit into any of previous described entities.
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Discussion

Vitamin D and PTH play a crucial role in calcium homeostasis in the human body. Conditions associated with low serum calcium and high PTH include pseudohypoparathyroidism, vitamin D deficiency and vitamin D resistance. This patient presented with symptoms of hypocalcemia and had normal 25 OH vitamin D and 1,25 OH vitamin D levels and high PTH levels. Initially a diagnosis of pseudohypoparathyroidism type 1b was made. Pseudohypoparathyroidism (PHP) is a group of heterogeneous disorders characterized by end organ resistance to parathormone due to defects in the GNAS locus encoding the α-subunit of stimulatory G protein. PHP type 1b presents with hypocalcemia and high parathormone levels but does not have the phenotypic features of classic Albright's Hereditary Osteodystrophy (AHO) that are found in type 1a PHP. Type 2 PHP is phenotypically similar to type 1b but exhibits an appropriate increase in cyclic AMP with PTH infusion suggesting that the defect must be downstream to the hormone-receptor interaction. Our patient’s hypocalcemia, low urine calcium, mild hyperphosphatemia and elevated PTH appeared at first to be consistent with PHP 1b or 2. What is unique to this case was the normal 1,25 vitamin D level. The PTH resistance and hyperphosphatemia that occurs in PHP is associated with a low concentration of 1,25 vitamin D, which was not seen in this case. Measured 1,25 vitamin D levels were similar whether the patient was on calcitriol replacement or not. Vitamin D3 and calcium supplementation did not improve calcium or parathormone levels during this therapy. Treatment with 0.25 mcg calcitriol twice a day (a relatively low dose), which did not change the 1,25 vitamin D level, led to immediate correction of calcium and PTH back to normal limits.

The only possible explanation for the findings in this case would be resistance to endogenous 1,25 vitamin D. Because endogenous 1,25 vitamin D and calcitriol are structurally identical the question remains how can there be resistance to the endogenous hormone but not to the exogenous hormone. Goff et al. showed contrasting effects of endogenous and exogenous 1,25 vitamin D on the regulation of vitamin D receptors (6). In an in vivo model induction of high levels of 1,25 by a low calcium diet did not result in up-regulation of vitamin D receptors whereas exogenous administration of 1,25 vitamin D increased receptor number by 1.5 to 3 fold. We hypothesize that despite normal 1,25 vitamin D levels she had a deficiency in the number of expressed vitamin D receptors that was corrected by the exogenous administration of 1,25 vitamin D. It is unclear why these symptoms appeared so late in life. The fact that she had evidence of osteopenia at her age suggests that her hypocalcemia may have been long standing. Symptoms may have developed because of a decrease exposure to sunlight and/or a decrease in her calcium intake. This, however, is only speculative. The other unanswered question is why despite hypocalcemia and hyperparathyroidism, both which stimulate 1-hydroxylation of 25-vitamin D, she did not have elevated 1,25 vitamin D levels.

Conclusion

This is a rare case of defective endogenous vitamin D responding to a trial of low dose calcitriol. We hypothesize that oral administration of active vitamin D increased the number of vitamin D receptors.

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Declaration of interest
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