“Calcimimetic" effect of alfacalcidol in a patient with unusual occurrence of familial hypocalciuric hypercalcemia (FHH) and primary hyperparathyroidism

EP038

Author: Mariana Costache Outas, MD, PhD

Hospital: Coltea Clinical Hospital, Endocrinology Outpatient Clinic, Bucharest, Romania

INTRODUCTION& OBJECTIVES

Heterozygous inactivating mutations of calcium sensory receptor (CASR) lead to familial hypocalciuric hypercalcemia (FHH), an asymptomatic autosomal dominant PTH-dependent hypercalcemic disease characterized by modest elevations in serum calcium (within 10% of the upper limit of normal), inappropriately serum PTH combined with low renal calcium excretion. Mutations confirmed in CASR, G protein alpha 11 (GNA11) and in the adapter related protein complex 2 sigma 1 subunit (AP2S1) genes are the molecular basis in the three subtype of FHH described to present. The differential diagnosis requires the distinction between FHH and primary hyperparathyroidism (HPT) due to a parathyroid adenoma and is based on the ratio of calcium to creatinine clearance below 0.01 in the FHH patients. Although the parathyroid glands may show moderate hyperplasia, the ultrasonography describes the normal size of parathyroid glands in FHH.

We report a case of concomitant occurrence of both FHH and HPT, after the parathyroid adenoma surgical resection, followed biochemically 12 months under treatment with vitamin D analog, alfacalcidol.

METHODS

We report the case of a 49 yr-old, caucasian woman with her first presentation in our clinic for mild asymptomatic hypercalcemia following surgery for parathyroid adenoma. Her personal history was positive for primary hypothyroidism (correctly substituted) due to the chronic thyroiditis and with long-lasting asymptomatic hypercalcemia not exceeding the level of total serum calcium of 11 mg /dL since 2006. In 2011 her hypercalcemia was worsened (maximum level 13.49 mg/dL, normal range 8.8-10.4) with high synchronously iPTH levels of 141 pg/mL (normal range 15-65). She was diagnosed with primary hyperparathyroidism due to a left inferior parathyroid adenoma, and the histopathological report confirmed the parathyroid adenoma with clear cell and scarce cytoplasm. Following elective surgical excision of the parathyroid adenoma (2016), her calcium levels remained slightly elevated with inappropriate PTH and low urinary calcium excretion. Her brother was known as papillary thyroid carcinoma and intermittent hypercalcemia with inappropriate PTH value when tested. She had mild vitamin D deficiency (22 ng/mL, normal range>30). The biochemical characteristics in her first evaluation and her follow up under replacement with vitamin D analog are shown in Table 1.

Table1. Parameters of calcium metabolism and their variation under treatment with alfacalcidol

	serum total Ca mg/dL (n.r)	uCa, mg/24h (n.r)	PTH, pg/mL (15-65)	Alfacalcidol (mcg/day)	FECa
baseline	10.8 (8.6-10)	84 (100-300)	20.61 (15-65)	0	0.0069
6 months	10.9 (8.6-10)	209 (100-300)	14.3 (15-65)	1	0.019
12 months	10.97 (8.8-10.4)	149 (100-300)	16. 1 (7.5-54)	0.5	0.014

n.r, normal range; u, urinary ; Ca, Calcium; PTH, parathormone; FECa, Calcium excretion fraction ($FECa=Ca_u*Cr_s/Ca_s*Cr_u$, blood and 24 urine parameters)

RESULTS

Urinary calcium excretion was highly dependent on alfacalcidol. A low dose of alfacalcidol provided a decreasing trend for total serum calcium due to its normal urinary excretion and PTH levels within normal range.

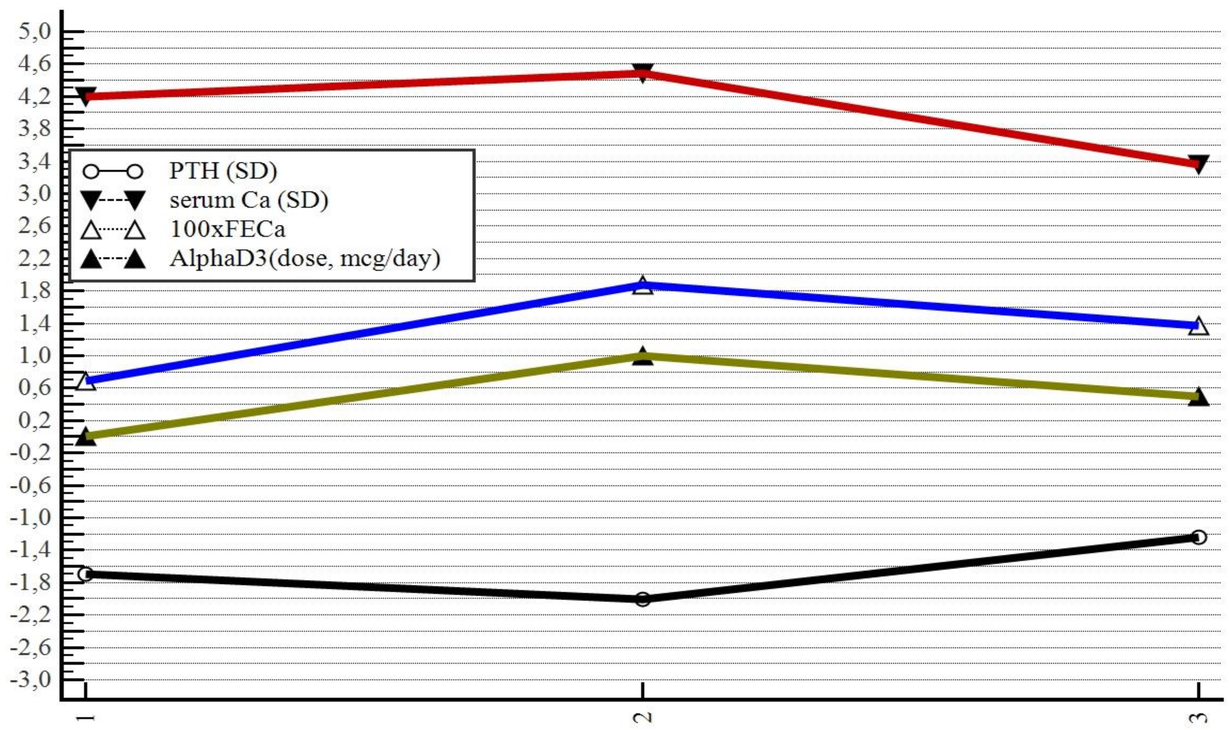

Figure 1. Variation of parameters at diagnosis (1) and under treatment with alfacalcidol for 6 (2) and 12 (3) months, respectively. PTH, parathormone (SD); serum Ca, total serum calcium (SD); FE, fractional excretion.

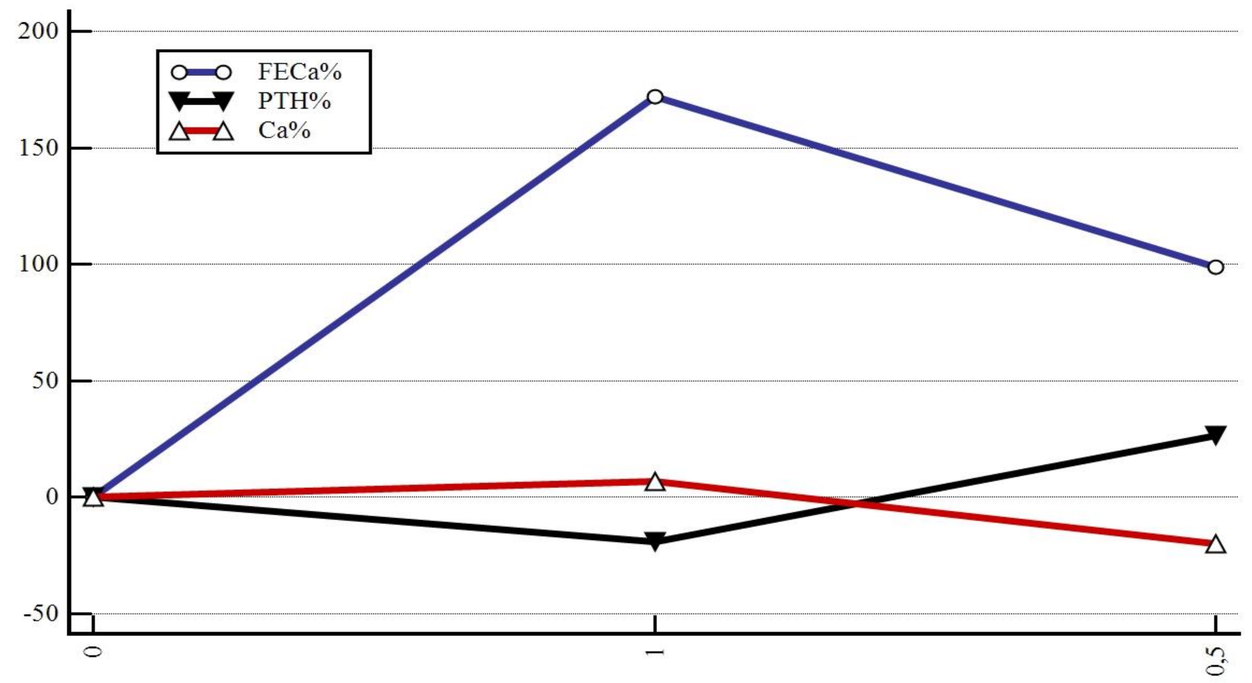

Figure 2. Relative change (%) of serum parameters from baseline (1) and following alfacalcidol treatment for 6 (2) and 12 (3) months. FECa, calcium clearance / creatinine clearance; PTH, parathormone; Ca, total serum calcium.

CONCLUSIONS

We reported the unusual occurrence of both familial hypocalciuric hypercalcemia (FHH) and primary hyperparathyroidism (HPT) in the same patient, and we investigated the potential effect on clinical management of alfacalcidol.

Decreased expression or function of the CaSR gene may play a role in the proliferation of parathyroid cells and the development of parathyroid adenomas.

Surgical intervention for concomitant HPT in FHH patients does not resolve hypercalcemia but is beneficial to reduce the degree of hypercalcemia, to alleviate the symptoms, and to prevent potential complications of hyperparathyroidism.

There are case reports on the use of calcimimetics in symptomatic FHH types I and III.

To our knowledge, this is the first report on the use of alfacalcidol, an active metabolite of vitamin D in an attempt to partially correct the mechanism involved in the etiopathogenesis of FHH.

REFERENCES:

- Egan, A. M., Ryan, J., Aziz, M. A., O’Dwyer, T. P., & Byrne, M. M. (2013). Primary hyperparathyroidism in a patient with familial hypocalciuric hypercalcaemia due to a novel mutation in the calcium-sensing receptor gene. Journal of Bone and Mineral Metabolism, 31(4), 477–480. http://doi.org/10.1007/s00774-012-0399-4
- Forde, H. E., Hill, A. D., & Smith, D. (2014). Parathyroid adenoma in a patient with familial hypocalciuric hypercalcaemia. Case Reports, 2014(oct15 1), bcr2014206473-bcr2014206473. http://doi.org/10.1136/bcr-2014-206473
- Frank-Raue, K., Leidig-Bruckner, G., Haag, C., Schulze, E., Lorenz, A., Schmitz-Winnenthal, H., & Raue, F. (2011). Inactivating calcium-sensing receptor mutations in patients with primary hyperparathyroidism. Clinical Endocrinology, 75(1), 50–55. http://doi.org/10.1111/j.1365-2265.2011.04059.x
- Vahe, C., Benomar, K., Espiard, S., Coppin, L., Jannin, A., Odou, M. F., & Vantyghem, M. C. (2017). Diseases associated with calcium-sensing receptor. Orphanet Journal of Rare Diseases, 12(1), 19. http://doi.org/10.1186/s13023-017-0570-z
- Wang, X. M., Wu, Y. W., Li, Z. J., Zhao, X. H., Lv, S. M., & Wang, X. H. (2016). Polymorphisms of CASR gene increase the risk of primary hyperparathyroidism. Journal of Endocrinological Investigation, 39(6), 617–625. http://doi.org/10.1007/s40618-015-0405-5

This poster was presented to BES Harrogate, 06 - 08 November 2017.