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Familial hypocalciuric hypercalcemia: grey zones of the differential diagnosis from primary hyperparathyroidism: a case report

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Abstract

Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant inherited disorder due to inactivating mutations in the calcium-sensing receptor (*CaSR*), less commonly in the G-protein subunit α11 (*GNA11*) or the adaptor-related protein complex 2, sigma 1 subunit (*AP2S1*) genes. It is characterized by mild to moderate hypercalcemia, hypocalciuria, and inappropriately normal or high PTH levels. The disorder is usually asymptomatic, and bone or renal involvement is rare. Adequate differential diagnosis between primary hyperparathyroidism and FHH is important to avoid unnecessary surgery. We report the case of a male patient with FHH showing biochemical heterogeneity to highlight the difficulties of differential diagnosis

Key Words hypercalcemia; familial hypocalciuric hypercalcemia; primary hyperparathyroidism; calcium-sensing receptor (CASR); parathyroid.

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Introduction

Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant inherited disorder due to heterozygous inactivating mutations in the calcium-sensing receptor (*CaSR*) gene, that encodes the sensor for extracellular calcium. CaSR is highly expressed on parathyroid cells, where it senses serum calcium concentration and regulates PTH secretion [1, 2]. Less commonly FHH is caused by mutation in the G-protein subunit α11 (*GNA11*) gene, encoding the GNA-11 protein, a GTP-binding transducer downstream the CaSR pathway, or in the adaptor-related protein complex 2, sigma 1 subunit (*AP2S1*) gene, that encodes clathrin-associated adaptor protein sigma 2 subunit 1 (AP2), a molecule involved in membrane recycling and internalization of CaSRs [3]. Loss-of-function mutations in these genes cause relative insensitivity to extracellular calcium in parathyroid cells and, thereby, shifts the set-point for suppression of PTH secretion to higher levels of serum calcium. As a consequence, serum calcium is higher than normal, whereas serum PTH is inappropriately normal or mildly elevated, i.e., it is not suppressed by hypercalcemia. Moreover, their mutated expression in the kidney causes increased renal tubular reabsorption of calcium and

magnesium with consequent hypercalcemia, hypocalciuria, and frequently high-normal levels of serum magnesium [1, 2, 4]. The disorder shows biochemical heterogeneity that can make challenging to differentiate patients with atypical presentations of FHH from primary hyperparathyroidism (PHP), mostly in the absence of family history, but this differential diagnosis is crucial to avoid unnecessary surgery [5]. We report the case of a male patient with FHH to highlight the difficulties of differential diagnosis.

Case report

A 73-year-old male with a long-lasting history of asymptomatic hypercalcemia was seen in the outpatient clinic of our University Hospital. At the age of 58 asymptomatic hypercalcemia was incidentally discovered at routine laboratory assessment, along with hypermagnesemia. In 2018, at the age of 70, hypercalcemia was found again and confirmed within the following 3 months (mean serum total calcium 11.6 mg/dl). PTH has been oscillating around the upper normal range with a mean level of 60.3 pg/dl, while 25OHD levels were in the normal reference range (Table 1). His past medical history was negative for lithiasis and/or nephrocalcinosis as well as renal failure, and significant for hypertension and diabetes under medical treatment with oral drugs (angiotensin receptor antagonists and metformin) at standard doses. Familial history was negative for endocrine disorders. At first evaluation he denied any symptoms attributable to hypercalcemia. Bone remodelling markers were within normal values (Table 1), bone mineral density (BMD) assessed by DXA was lower than average for his age consistently with osteopenia (T-score -2.0 at the lumbar spine and femoral neck) and no fragility fracture were documented at dorsal and lumbar spine X-rays. The patient underwent neck ultrasonography (US) which revealed a 10x7x7-mm hypoechoic nodule, in a position corresponding to the lower pole of the right thyroid lobe, suggesting a hypertrophic parathyroid gland (Fig. 1). No abnormal lymph nodes were detected in the neck. Dual phase parathyroid scintigraphy with 99mTc-methoxyisobutylisonitrile (99mTc-MIBI) failed to reveal any abnormal tracer uptake in a position corresponding to the parathyroid gland mass revealed at US as well as in other sites (Fig. 1). The patient was diagnosed with a primary hyperparathyroidism and candidate for parathyroid surgery, that he refused. Serum calcium monitoring was recommended.

Three years later, in 2021 at the age of 73-year, the patient was seen in our outpatient clinic. In the previous years, the levels of serum calcium had remained stable above the normal limit (mean serum total calcium 11.2 mg/dl). A neck US had not confirmed the previous finding of a hypoecoic nodule (10 mm in maximum diameter) at the lower pole of the right thyroid lobe, attributed to hypertrophic parathyroid at first evaluation. Once again he did not complain of any symptoms and/or signs related to hypercalcemia. Biochemical evaluation confirmed moderately elevated

levels of both total and ionized serum calcium associated to normal levels of PTH and vitamin D in multiple determinations. Urinary parameters on a 24h sample were evaluated and 24-h-urinary calcium was found to be low while calcium to-creatinine clearance ratio (Ca/Cr) was always less than 0.01 (Table 1). The patient denied any treatment interfering with calcium metabolism/clearance, but he had been advised by his general practitioner to limit dietary calcium intake due to the persistent hypercalcemia. These findings raised the suspicious of FHH. However, when evaluating his family tree, we found that the parents were deceased and his only daughter was found to had normal serum calcium and PTH values. Unfortunately, the patient refused to undergo genetic testing. Therefore, in the absence of a family history of hypercalcemia and positive genetic tests, the diagnosis of FHH couldn't be confirmed, remaining hypothetical.

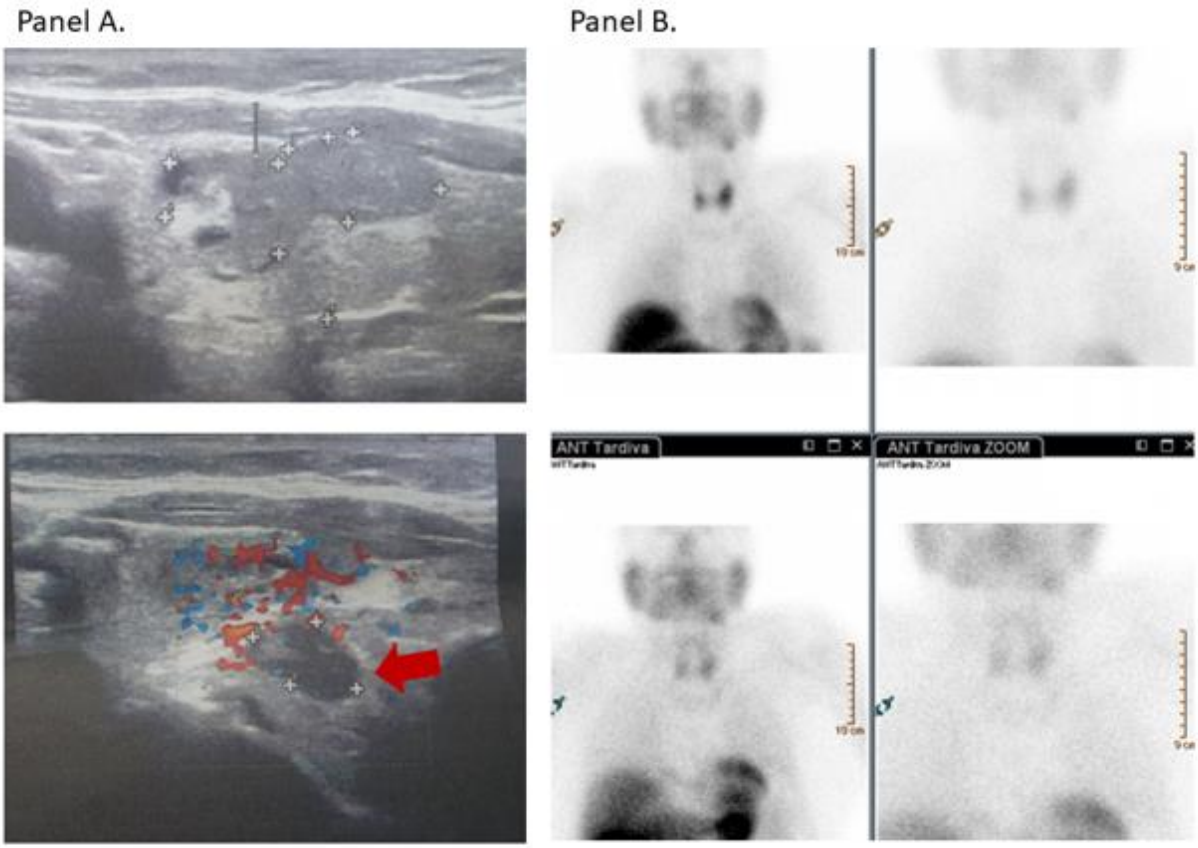
Table 1. Illustrative biochemical data of our male patient at first evaluation in 2018 and three years later in 2021.

	June 2018	**February 2021**
Total calcium (*8.2–10.4)*	**11.7 mg/dl**	**11.2 mg/dl**
Ionized calcium *(1.10-1.30)*	**1.4 mmol/L**	**1.4 mmol/L**
Phosphorus *(2.5-4.6)*	3.1 mg/dl	2.7 mg/dl
PTH* *(12-62)*	**88.80 pg/ml**	38.80 pg/ml
Vitamin D *(30-100)*	41.5 µg/dl	55 µg/dl
Creatinine *(0.5-1.4)*	0.85 mg/dl	0.85 mg/dl
Magnesium (*1.5-3.8)*	3.8 mg/dl	**3.9 mg/dl**
Total proteins (*6-8.2)*	6.9 g/dl	7.6 g/dl
Osteocalcin (*10.7-34.1)*	29 ng/ml	18,9 ng/dl
CTX *(0.115-0.748)*	0.377 µg/L	0.587 µg/l
Alkaline phosphatase *(40-150)*	54 UI/L	49 UI/L
TSH *(0,300-4,200)*	2.114 uUl/ml	2.08 uUl/ml
FT4 *(9,00-16,00)*	12.17 pm/L	13.20 pm/L
Calcitonin *(v.n. <11.4*)	0.02 pg/ml	/
Urinary-24h-calcium *(100-300)*	120 mg/24 h (1.3 mg/kg/24h)	**48 mg/24h (0.53 mg/kg/24h)**
Urinary-24h- Phosphorus *(400-1300)*	960 mg/24h	648 mg/24h

Urinary creatinine *(0.8-2.0)*	/	0.88 g/24h
Ca/Cr Cl	/	**0.0046**

In brackets normal values. Boldface values indicate abnormality.
* Serum intact PTH was measured using a solid-phase, two-site chemiluminescent enzyme labelled immunometric assay (Immulite 2000).
** calcium to-creatinine clearance ratio

Fig.1 Panel A. Neck ultrasonography (US) demonstrating a multinodular goiter (top) and a hypoechoic nodule of 10 mm in maximum diameter in the lower portion of the left thyroid lobe (bottom, red arrow), suggesting a hypertrophic parathyroid gland. Panel B. Dual phase parathyroid scintigraphy with 99mTc-MethoxyIsobutylIsonitrile (MIBI). Planar images of the neck and thoracic regions (10 minutes per frame) were acquired 10 min (A) and 120 min (B) after i.v. administration of 370 MBq of ^{99m}Tc-MIBI (magnification 1 and 2, matrix 265×256 and 128×128, respectively). Images were obtained using a dual-headed gamma-camera equipped with low-energy high-resolution parallel-hole collimator (LEHRPAR). A photopeak of 140 KeV with symmetrical 20% window was used. No focal areas of abnormal tracer uptake were appreciated in a position corresponding to the left parathyroid gland mass revealed at US nor in other sites



Discussion.

FHH is generally a benign disorder characterized by a lifelong hypercalcemia, which remains quite stable over the years. While other conditions causing hypercalcemia are associated with significant morbidity and mortality, FHH generally follows a benign course. Most patients are asymptomatic and no renal or bone complications occur, only a few patients complaining of symptoms (muscle weakness, fatigue, arthralgias and increased thirst) or developing more severe complications (for instance, pancreatitis). Patients and their relatives should be reassured that the disorder is not

progressive, and rarely associated with complications, to avoid excess monitoring and unnecessary parathyroid surgery, that is not required in the case of FHH.

A key point is represented by the differential diagnosis with other conditions causing hypercalcemia, mainly PHP. Indeed, failure to diagnose FHH can result in unwarranted surgery for the mistaken diagnosis of PHP, given the possible overlap of biochemical features due to the heterogeneity of both disorders. The characteristic parameter for discriminating between FHH from PHP is calcium excretion in 24-h urine, which is typically low in FHH patients and high in PHP patients. For this reason, it is important to include 24-h urine calcium and creatinine measurement in the initial workup of hypercalcemia. However, overlap still exists since both FHH and PHP patients may exhibit urinary calcium levels within normal range [6,7]. In our patient, for instance, serum PTH was moderately increased and urinary calcium within normal values (even if lower than 200 mg/24h) at first evaluation. Moreover, the patient was diagnosed with hypercalcemia at the age of 63 and his family his history was negative. For these reason, FHH was not suspected and the patient was wrongly diagnosed with PHP and candidate to a surgical exploration, that would turn to be not useless. As in the case of our patient, fractional calcium excretion may aid in differentiating the two conditions. It is calculated as follows: [Urinary Calcium × Serum Creatinine] / [Serum Calcium × Urinary Creatinine], all in mg/dl. The Ca/Cr clearance ratio is < 0.01 in about 80% of cases of FHH, while a similar or higher proportion of patients with PHP have values > 0.02 [7]. However, there may be considerable biochemical overlap with PHPT, as ~20% of FHH patients have a CCCR above this threshold, whilst 10-20% of PHPT patients have a CCCR below this cut-off [8, 9]. Distinguishing between FHH and PHP is more difficult in the absence of a family history of hypercalcemia, if PTH levels are increased and if the Ca/Cr clearance ratio is greater than 0.01 and less than 0.02 [8]. A familial history of hypercalcemia, detection of asymptomatic hypercalcemia before the age of 40, as well as a personal and/or familial history of persistent hypercalcemia after parathyroid surgery, favours the diagnosis of FHH. Obtaining serum calcium values from first-degree relatives in the absence of a family history can be helpful. Genetic studies are mandatory to confirm the diagnosis. Finally, other causes of hypocalciuric hypercalcemia should be ruled out, such as vitamin D deficiency, very low calcium dietary intake, mild renal insufficiency, and medical therapies (thiazide diuretics or lithium). Correction of any of these conditions will lead to hypercalciuria if the patient has PHPT but not in FHH patients [7].

In conclusion, the differentiation of FHH from PHP may be difficult, but it is essential in order to prevent ineffective surgical procedures and unnecessary and expensive monitoring. The diagnosis of FHH cannot be based only on suggestive biochemical data (long-lasting, not progressive mild

hypercalcemia and CCCR <0.01), but it should be confirmed by means of genetic studies. In the absence of a family history of hypercalcemia and of confirmatory genetic tests, the diagnosis of FHH remains uncertain. In uncertain cases one should consider the very low prevalence of FHH as compared to PHPT. Nonetheless, physicians should be cautioned to send such uncertain cases of mild asymptomatic hypercalcemia to parathyroidectomy just because PHPT is more common, and FHH should be considered. Finally, physician should be aware that patients with FHH may be more sensitive than normal subjects to calcium or vitamin D toxicity, and ubiquitous vitamin D supplementation should be avoided.

Ethical disclosures

Conflict of Interest: The Authors declare that they have no conflict of interest.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the patient. This study does not contain any studies with animals performed by any of the authors.

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References

1. Lee, J.Y., Shoback, D.M. (2018). Familial hypocalciuric hypercalcemia and related disorders. Best Pract Res Clin Endocrinol Metab, 32(5):609-619.
2. Tfelt-Hansen, J., Brown, E.M. (2005). Calcium-sensing receptor in normal physiology and pathophysiology: a review. Crit Rev Clin Lab Sci, 42(1):35-70.
3. Szalat, A., Shpitzen, S., Tsur, A., Zalmon Koren, I., Shilo, S., Tripto-Shkolnik, L., Durst, R., Leitersdorf, E., Meiner, V. (2017). Stepwise CaSR, AP2S1, and GNA11 sequencing in patients with suspected familial hypocalciuric hypercalcemia. Endocrine, 55(3):741-747. doi: 10.1007/s12020-017-1241-5
4. Hovden, S., Rejnmark, L., Ladefoged, S.A., Nissen, P.H. (2017). AP2S1 and GNA11 mutations - not a common cause of familial hypocalciuric hypercalcemia. Eur J Endocrinol, 176(2):177-185. doi: 10.1530/EJE-16-0842.
5. Riccardi, D., Brown, E.M. (2010). Physiology and pathophysiology of the calcium-sensing receptor in the kidney. Am J Physiol Renal Physiol, 298(3): F485-99.
6. Marx, S.J. (2018). Familial Hypocalciuric Hypercalcemia as an Atypical Form of Primary Hyperparathyroidism. J Bone Miner Res, 33(1):27-31. https://doi.org/10.1002/jbmr.3339
7. Shinall, M.C.Jr, Dahir, K.M., Broome, J.T. (2013). Differentiating familial hypocalciuric hypercalcemia from primary hyperparathyroidism. Endocr Prac, 19(4):697-702. https://doi.org/10.4158/EP12284.
8. Moore, E.C., Berber, E., Jin, J., Krishnamurthy, V., Shin, J., Siperstein, A. (2018). Calcium creatinine clearance ratio is not helpful in differentiating primary hyperparathyroidism from familial herpercalcemic hypocalciuria: a study of 1000 patients. Endocr Pract, 24: 1-7.
9. El-Hajj, F.G. Familial Hypocalciuric Hypercalcemia and Neonatal Severe Hyperparathyroidism. In: The Parathyroids. 2014. Editors: Bilezikian, J.P., Marcus, R., Levine, M.A., Marcocci, C., Silverberg, S., Potts, J.T. Academic Press, 2014

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