Available online at www.medicinescience.org

Medicine Science International Medical Journal

CASE REPORT

Medicine Science 2022;11(4):1731-3

A girl diagnosed with familial hypocalciuric hypercalcemia with heterozygous p.Cys575Tyr variation in the CaSR gene

Ismail Dundar[1], Emine Camtosun[1], Mustafa Dogan[2], Leman Kayas[1], Nurdan Ciftci[1], Aysehan Akinci[1]

Inönü University, Faculty of Medicine, Department of Pediatric Endocrinology, Malatya, Türkiye
Başakşehir Cam and Sakura City Hospital Medical Genetics Clinic, Istanbul, Türkiye

Received 22 August 2022; Accepted 06 November 2022
Available online 28.11.2022 with doi: 10.5455/medscience.2022.08.193

Abstract

Familial hypocalciuric hypercalcemia (FHH) is a benign disease associated with heterozygous inactivating mutations in the calcium-sensing receptor (CaSR) gene. This article presents a girl with heterozygous p.Cys575Tyr variation in the CaSR gene. The serum calcium level of a 9.2-year-old girl was 12.4mg/dl in incidental laboratory analysis. On the same occasion, the serum parathyroid hormone (PTH) level was 45 pg/ml, 25(OH) vitamin D level 24.2ng/ml, 1.25 dihydroxy vitamin D level 22pg/ml, and urinary Ca/creatinine ratio <0.01. The ultrasonographic evaluation of the urinary system was unremarkable. The clinical and laboratory findings pointed towards FHD. A heterozygous p.Cys575Tyr (c.1724G>A) variation was detected in the patient's CaSR gene, which was reported before, but no clinical manifestations were specified. In children with asymptomatic hypercalcemia, the diagnosis of FHH should be considered if the PTH level is normal or high and the urinary calcium is low.

Keywords: Hypercalcemia, familial hypocalciuric hypercalcemia, calcium-sensing receptor (CaSR)

Introduction

Familial hypocalciuric hypercalcemia or familial benign hypercalcemia (FHH) is an inherited disease that involves lifelong hypercalcemia, usually mild, and resistance of hypercalcemia to subtotal parathyroidectomy [1]. FHH is encountered in 3 types. FHH1 is caused by loss-of-function mutations of the calcium-sensing receptor (CaSR) [2], type 2 FHH is caused by inactivating mutations in the GNA11 gene, which encodes the G-protein a11 subunit [3], and type 3 FHH is caused by inactivating mutations in the AP2S1 gene encoding the sigma 1 (AP2s) subunit [4]. While the phenotypes of these different subtypes of FHH are generally similar, some cases of type 3 FHH carrying the AP2S1 mutation are more symptomatic [5]. Type 1 FHH is characterized by mild to moderately elevated serum calcium levels, inappropriately elevated serum parathormone, and decreased daily urinary calcium excretion [6]. Most cases of type 1 FHH do not require any treatment. However, recent studies have suggested that calcimimetic drugs can be used when treatment is needed [7]. This article reports a case thought to have familial hypocalciuric hypercalcemia due to moderate hypercalcemia, inappropriate normal parathormone level, and a marked decrease in daily urinary calcium excretion, and diagnosed with heterozygous p.Cys575Tyr(c.1724G>A) variation in the CaSR gene in the genetic study, which has been reported in the literature before, but no clinical manifestations were specified.

CASE REPORT

A 9.2-year-old girl with no pre-existing disease was evaluated because of her short stature, and hypercalcemia was detected coincidentally in her biochemistry tests. Thereupon, she was examined for the etiology of hypercalcemia. Detailed history taking and systems examination revealed no complaints that could be associated with hypercalcemia. There was no consanguinity between the mother and father, and the patient was born 3300 grams by normal vaginal delivery following an uneventful pregnancy and

*Corresponding Author: Ismail Dundar, Inonu University, Faculty of Medicine, Department of Pediatric Endocrinology, Malatya, Türkiye
E-mail: ismail.dundar@inonu.edu.tr

had normal neuromotor development. She had one healthy sibling. There was no family history of kidney stones or hypercalcemia.

Discussion

Familial hypocalciuric hypercalcemia (AHH) is an autosomal dominant disease that develops due to an inactivating heterozygous mutation in the calcium-sensitive receptor (CASR) gene on the third chromosome. Biochemical findings are very low urinary calcium excretion, slightly increased magnesium levels, normal or somewhat increased parathormone (PTH) levels, normal vitamin D levels, and moderately increased serum calcium (Ca+) levels [2,8,9]. CaSR (Calcium sensing receptor) is a G-protein coupled receptor that plays an essential role in maintaining calcium homeostasis [10]. It has been suggested that the calcium balance setpoint shifts to higher values with decreased sensitivity of the CaSR receptor. This situation is incompatible with hypercalcemia, and a decrease in calcium excretion in the urine is observed with an increase in parathormone levels [6,11]. The most prominent laboratory disorder is hypocalciuria. A daily urinary calcium-creatinine clearance ratio of <0.01 is diagnostic [12]. Considering the clinical and biochemical overlap with primary hyperparathyroidism cases, genetic testing for GNA11 and AP2S1 should be performed primarily if the CASR gene and CASR gene are negative for suspected FHH cases [8].

The patient, who applied to our clinic due to short stature and coincidentally found to have hypercalcemia, initially suggested primary hyperparathyroidism due to the inappropriately suppressed serum parathormone levels. However, the lack of a clinical picture of hypercalcemia and the urine calcium/creatinine clearance ratio <0.01 made us think of the diagnosis of FHD. No nephrocalcinosis and/or nephrolithiasis was detected in the kidney USG. Also, no osteopenia was observed on direct radiographs. Regarding FHH with autosomal dominant inheritance, the serum calcium levels of the parents and siblings were normal. There was no family history of fractures or kidney stones. Hypercalciuria can be observed due to being thyrotoxic when urine calcium is examined or because of medications such as furosemide [13,14]. Our patient was euthyroid when her urinary calcium/creatinine clearance ratio was measured, and she did not have a history of drug use.

Hypercalcemia in AHH is usually mild, and therefore, these patients can live for a long time undiagnosed without causing any clinical disorder [8]. In the follow-up of our case, saline twice the maintenance fluid and furosemide at 1 mg/kg/dose every 6 hours were administered intravenously for 3 days. Since the serum Ca level did not decrease adequately with these treatments, pamidronate infusion at an amount of 0.5 mg/kg/day was initiated. With this therapy, the serum Ca level could only decrease to 11.7 mg/dl. The blood calcium increased again to 12.4mg/dl after two weeks. In the genetic study for FHH disease, heterozygous p.Cys575Tyr(c.1724G>A) variation was detected in the patient's CaSR gene. This variant was associated with familial hypocalciuric hypercalcemia phenotype with clinical significance (Accession Number: VCV000410335) in ClinVar in 2016, but detailed data were not shared (Table 2). The literature search revealed no other case with this variant. This report contributes to the literature by presenting the clinical and laboratory findings of our case in detail. Furthermore, no variation was detected in the genetic analysis of the parents.

In FHH, no special treatment is required because calcium is not usually very high and does not cause symptoms, and kidney complications are not expected due to hypocalciuria. Cinacalcet is a positive allosteric modulator of CASR. Calcium levels may return to normal levels in patients with FHD who use this drug. Cinacalcet can be used in patients with FHH who have symptoms suggestive of hypercalcemia or hyperparathyroidism (11,13,14,15). No progressive skeletal demineralization or renal injury was observed, and thus, our patient is followed up without any treatment.

Table 1. Laboratory values of the patient during diagnosis and follow-up

	Ca (mg/dl)	P (mg/dl)	Mg (mg/dl)	ALP (U/L)	PTH (pg/mL)	Vitamin D [25(OH)D] ng/ml	Spot Urine Ca/Cr ratio
At diagnosis	12.4	3.5	2.4	263	45	24.2	0.01
3rd week	12.93	2.86	2.9	233	37.4	15.8	0.01
6th week	12.38	2.83	2.5	250	42	12.8	0.01
9th month	12	3.2	2.5	273	51.4	-	0.012
12th month	12.3	2.9	2.5	324	50.4	12.6	0.01

Ca: Calcium, P: phosphorus, Mg: magnesium, ALP: alkalen fosfataz, PTH: parathyroid hormone, Ca/Cr ratio: calcium to creatinin ratio

Table 2. The entire exome dataset including Genome Aggregation Database (gnomAD), conservation score (GERP), predictions of pathogenicity based on ACMG recommendations

GENE	**CASR**
Transcript ID	NM_001178065.2
dbSNP	rs1553768736
Variant	c.1724G>A (p.Cys575Tyr)
Variant location	Exon 6
Variant type	Missense
MutationTaster	Disease-causing
PROVEAN	Damaging
SIFT	Damaging
gnomAD (exomes)	Not found
ClinVar	Uncertain significance
Conservation	Conserved
DANN score	0.9905
GERP score	NR: 6.17; RS: 6.17
ACMG classification	Likely pathogenic
ACMG pathogenicity criteria	PM1, PM2, PP2, PP3

gnomAD: Genome Aggregation Database ACMG: The American College of Medical Genetics and Genomics

Conclusion

Familial hypocalciuric hypercalcemia is a benign disease that does not cause any complications. In most cases, calcium and PTH levels remain stable. Although it is among the rare causes, AHH should be kept in mind when investigating the etiology of hypercalcemia. To confirm the diagnosis, it is recommended to determine the type of CaSR gene inactivating mutation by genetic analysis.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Informed consent
Informed consent forms were obtained from the parents of the patients for publication of the cases, including images.

References

1. Marx SJ. Calcimimetic Use in Familial Hypocalciuric Hypercalcemia-A Perspective in Endocrinology. J Clin Endocrinol Metab. 2017;102:3933-3936.

2. Dershem R, Gorvin CM, Metpally RPR, et al. Regeneron Genetics Center. Familial Hypocalciuric Hypercalcemia Type 1 and Autosomal-Dominant Hypocalcemia Type 1: Prevalence in a Large Healthcare Population. Am J Hum Genet. 2020;106:734-47.

3. Nesbit MA, Hannan FM, Howles SA, et al. Mutations affecting G-protein subunit α11 in hypercalcemia and hypocalcemia. N Engl J Med. 2013;368:2476-86.

4. Nesbit MA, Hannan FM, Howles SA, et al. Mutations in AP2S1 cause familial hypocalciuric hypercalcemia type 3. Nat Genet. 2013;45:93-7.

5. Hannan FM, Howles SA, Rogers A, et al. Adaptor protein-2 sigma subunit mutations causing familial hypocalciuric hypercalcaemia type 3 (FHH3) demonstrate genotype-phenotype correlations, codon bias and dominant-negative effects. Hum Mol Genet. 2015;24:5079-92.

6. Brown EM. Clinical lessons from the calcium-sensing receptor. Nat Clin Pract Endocrinol Metab. 2007;3:122-33.

7. Mayr B, Schnabel D, Dörr HG, Schöfl C. GENETICS IN ENDOCRINOLOGY: Gain and loss of function mutations of the calcium-sensing receptor and associated proteins: current treatment concepts. Eur J Endocrinol. 2016;174:R189-208.

8. Lee JY, Shoback DM. Familial hypocalciuric hypercalcemia and related disorders. Best Pract Res Clin Endocrinol Metab. 2018;32:609-19.

9. Christensen SE, Nissen PH, Vestergaard P, et al. Discriminative power of three indices of renal calcium excretion for the distinction between familial hypocalciuric hypercalcaemia and primary hyperparathyroidism: a follow-up study on methods. Clin Endocrinol (Oxf). 2008 Nov;69:713-20.

10. Kim ES, Kim SY, Lee JY, et al. Identification and functional analysis of a novel CaSR mutation in a family with familial hypocalciuric hypercalcemia. J Bone Miner Metab. 2016 Nov;34:662-7.

11. Lee JY, Shoback DM. Familial hypocalciuric hypercalcemia and related disorders. Best Pract Res Clin Endocrinol Metab. 2018;32:609-19.

12. Marx SJ. Letter to the editor: Distinguishing typical primary hyperparathyroidism from familial hypocalciuric hypercalcemia by using an index of urinary calcium. J Clin Endocrinol Metab. 2015 Feb;100:L29-30.

13. Minisola S, Pepe J, Piemonte S, Cipriani C. The diagnosis and management of hypercalcaemia. BMJ. 2015;350:h2723.

14. Moore EC, Berber E, Jin J, Krishnamurthy V, Shin J, Siperstein A. Calcium-creatinine clearance ratio is not helpful in differentiating primary hyperparathyroidism from familial hypercalcemic Hypocalciuria: a study of 1,000 patients. Endocrine Practice. 2018;24:988-94.

15. Hannan FM, Kallay E, Chang W, Brandi ML, Thakker RV. The calcium-sensing receptor in physiology and in calcitropic and noncalcitropic diseases. Nat Rev Endocrinol. 2018;15:33-51.