Case report: familial hypocalciuric hypercalcemia

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Background: Familial hypocalciuric hypercalcemia (FHH) is a hypercalcemic syndrome that is usually characterized by uncomplicated hypercalcemia and normal longevity. The inheritance pattern is autosomal dominant with high penetrance, and it affects both men and women equally. FHH is caused by mutations that disturb the normal functioning of the calcium-sensing receptor (*CaSR*) gene. This causes a general lack of sensitivity to calcium, eventually leading to hypercalcemia and low calcium levels in the urine.

Case Description: We report a case of a healthy 24-year-old female with longstanding hypercalcemia and a family history indicating asymptomatic hypercalcemia. The patient was also asymptomatic and had no significant past medical or surgical history. Laboratory investigations and the genetic study revealed findings suggestive of FHH subtype 1.

Conclusions: The phenotype of FHH is normal, and symptoms of hypercalcemia are usually not present. Patients with FHH and hypoparathyroidism have lower calcium clearance than controls with hypoparathyroidism. This shows that relative hypocalciuria in FHH is not caused by hyperparathyroidism. Since calcium does not appropriately suppress or affect the parathyroid glands in FHH, this means that FHH is a disorder of abnormal transport of extracellular calcium and/or response to it in at least two organs, the parathyroid gland and the kidney. It is quite similar to primary hyperparathyroidism (pHPT) biochemically hence it is important to differentiate this condition from pHPT and hypercalcemia caused by other diseases to avoid any unnecessary surgical or medical intervention.

Keywords: Familial hypocalciuric hypercalcemia (FHH); asymptomatic; hypercalcemic; calcium; case report

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Introduction

Familial hypocalciuric hypercalcemia (FHH) is a rare and genetically heterogeneous condition. It is clinically characterized by mild to moderate hypercalcemia reliant on parathyroid hormone (PTH), an autosomal dominant inheritance pattern, and normal to reduced calcium excretion in the urine (1). Patients have hypercalcemia, decreased urinary calcium, elevated magnesium levels, and low phosphate levels. PTH level is either normal or just slightly raised. FHH is a rare condition that is passed down in an autosomal dominant pattern that affects both men and women equally. Specific prevalence is not known but is estimated to be between 1 in 78,000 and 1 in 1,000, which is much lower than the prevalence of primary hyperparathyroidism (pHPT), which is 1 in 1,000. However,

the true prevalence is likely to be higher because many individuals suffering from it are unaware of its presence (2).

FHH is usually classified into three types. FHH type 1 is the most common, affecting almost more than 65% of patients. It is caused by mutations in the calcium-sensing receptor (CaSR) (3). Type 2 of FHH is responsible for causing heterozygous germline loss-of-function of G-protein subunit α-11 (4). While about 20% of instances result in FHH3, which is caused by missense mutations affecting the codon Arg15 (p.R15) in adaptor-related protein complex 2 subunit sigma 1 (AP2S1) (5). In comparison to pHPT, which is marked by elevated calcium excretion in urine, FHH is represented by relatively reduced urinary calcium levels and normal plasma 25-hydroxyvitamin D levels with normal seasonal changes while plasma 1,25-dihydroxy vitamin D levels, on the other hand, are slightly higher than normal. Even though there is a little more bone turnover, the Z-scores for bone mineral density are normal. Differential diagnoses include mostly primary hyperthyroidism, but sometimes also hypercalcemia due to malignancy and use of thiazide diuretics (6).

Since is a benign condition, patients are usually advised against parathyroidectomy. Complications of pHPTs, such as osteopenia and nephrolithiasis, do not affect people suffering from FHH and instead, the rates are the same as in the general population. Babies with homozygous CaSR mutations sometimes have a severe form of this disease which is referred to as neonatal severe pHPT and is quite a rare condition. Although FHH is rare, it is an important cause of hypercalcemia, especially in younger people. It is important to diagnose this condition, not just in the reporting patient but also in other family members, because surgery should not be performed in such patients (7). We report a case of 24-year-old female patient diagnosed with FHH after genetic testing. We present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-23-132/rc).

Highlight box

Key findings

- In our patient, who presented with the concern of unexplained hypercalcemia, genetic testing was performed, which showed a genetic abnormality involving the calcium-sensing receptor gene on chromosome 3 and confirmed the diagnosis of familial hypocalciuric hypercalcemia (FHH) type 1. Hence, unnecessary surgical or pharmacological intervention was successfully avoided.

What is known and what is new?

- FHH is a rare condition and shows a striking resemblance to primary hyperparathyroidism (pHPT), which often results in the misdiagnosis of FHH cases. However, the pathophysiology of both of these conditions is different; they share similarities in terms of biomarkers such as serum calcium, chloride, magnesium, and parathyroid hormone. It is critically important to distinguish between these two conditions since FHH, unlike pHPT, does not require intervention as it is not associated with serious complications in most cases, although on the other hand, management of pHPT involves parathyroidectomy.
- Through this case report, we highlight the role and importance of genetic testing for the confirmatory diagnosis of FHH so unneeded parathyroidectomies can be effectively avoided.

What is the implication, and what should change now?

- When patients present with the concern of hypercalcemia in routine clinical practice, along with identifying pHPT, clinicians should also investigate the incidence of FHH through genetic testing before planning any intervention for the patients with hypercalcemia, especially in asymptomatic hypercalcemic cases.

Case presentation

A healthy 24-year-old female patient presented to The Medical Endocrinlogy Clinic at King Fahad Hospital in Al Ahsa, eastern Saudi Arabia with a complaint of unexplained chronic hypercalcemia for which she further requested a referral to the more specialized local national health center. She reported no notable clinical manifestations, including headache, constipation, abdominal pain, or personality change. She had no history of renal stones, fractures, or abnormal gait. During her routine medical checkup, she was incidentally diagnosed with hypercalcemia. The patient gave a non-detailed family history of hypercalcemia that involves paternal side relatives. She expressed concern about her elevated serum calcium levels and expected more evaluation. The patient did not report any significant medical or surgical history. Clinically, she was not in distress and all her vitals were normal. She had a body mass index (BMI) of 22 kg/m^2. She had no evidence of neck swelling. Other systemic evaluations including neurological examination, revealed no signs of hypercalcemia. Laboratory results of the patient indicated high serum calcium, high serum PTH, normal serum alkaline phosphatase, and normal serum phosphorus and magnesium with very low serum vitamin D_3 levels. The patient's 24-hour urine collection sample showed a calcium/creatinine clearance ratio was 0.001 (*Table 1*). The patient is a mother of three children, 3-year-

Table 1 The results of serum laboratory investigations

Serum & urine biochemistry	Value	Normal reference range
Total serum calcium, mmol/L	3.2	2.18–2.58
Serum albumin, g/dL	43.3	30–50
Serum corrected calcium, mmol/L	3.3	2.18–2.58
Serum phosphorus, mmol/L	0.8	0.8–1.5
Serum magnesium, mmol/L	0.86	0.6–1.1
Serum parathyroid hormone, pmol/L	33.4	1.59–7
Serum alkaline phosphatase, U/L	58	50–136
Serum creatinine, µmol/L	90	50–90
Serum 25(OHD), ng/mL	6.75	20–40
Urinary calcium/creatinine clearance ratio	0.0079	More than 0.02

25(OHD), 25-hydroxy-vitamin D.

Table 2 Laboratory investigation of case series, including first generation

Case series	Serum concentration						
	Ca^{++}, mmol/L	$PO4^{-}$, mmol/L	Mg^{++}, mmol/L	PTH, pmol/L	ALP, U/L	Albumin, g/dL	25(OHD), ng/mL
Patient's father	2.98	1.30	0.80	2.15	122	40	25.2
Index case (patient)	3.2	0.82	0.86	33.4	58	43	6.75
Patient's sibling	3	0.71	0.88	7.09	109	40	12.97
Patient's twin boy 1	3.5	1.33	0.99	1.34	596	41	39.55
Patient's twin boy 2	3.4	1.34	1.04	3.07	601	41	28.66
Patient's daughter	3.2	1.32	0.97	4.74	333	41	8.16

Ca^{++}, calcium; $PO4^{-}$, phosphorous; Mg^{++}, magnesium; PTH, parathyroid hormone; ALP, alkaline phosphatase; 25(OHD), 25-hydroxy-vitamin D.

old twin boys, and a 5-year-old daughter. Both the twin boys were referred to a local national highly specialized health center immediately after birth due to incidental findings of high serum calcium without any clinical manifestations although the 5-year-old daughter is under evaluation for hypercalcemia with no evidence of clinical manifestations. Laboratory investigation results of the Patient's sibling, children and father are illustrated in (*Table 2*). A genetic study was performed for our patient, and it revealed a genetic abnormality involving the *CaSR* gene in chromosome number 3 which is highly suggestive of FHH1. Genetic study results are summarized in (*Table 3*). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient and her relevant family member for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

FHH is also referred to as Marx's syndrome and was first reported by Jackson and Boonstra in the year 1966 (8). CaSR determines the calcium level present extracellularly and modifies the calcium level in urine along with the synthesis and excretion of PTH. Hence, when the calcium level in the blood rises, there is reduced synthesis of PTH and increased excretion of calcium in the urine. In FHH, the inactivating mutation halts the function of CaSR which affects many different tissues. When there is more ionized calcium in the blood, the parathyroid cells become less

Table 3 Genetic study of the patient (index case)

Genetic test	Result
Chromosome locus	3q21.1
Defected gene	*CaSR* protein gene
DNA change	c.554 G>A
Protein change	R185Q heterozygous affected autosomal dominant
Predicted effect on gene/gene function	An amino acid substitution alter protein function

CaSR, calcium-sensing receptor.

sensitive. In fact, PTH is still made even when the calcium level in the blood is high, and it takes elevated calcium levels in the blood to inhibit the production of PTH (9). Patients with FHH and hypoparathyroidism have lower calcium clearance than controls with hypoparathyroidism. This shows that relative hypocalciuria in FHH is not caused by hyperparathyroidism. Since calcium does not appropriately suppress or affect the parathyroid glands in FHH, this means that FHH is a disorder of abnormal transport of extracellular calcium and/or response to it in at least two organs, the parathyroid gland and the kidney (10).

Because both conditions can present as hypercalcemia with normal or elevated levels of PTH, FHH can frequently be confused with pHPT. Numerous markers of renal calcium excretion have been developed to distinguish the two diseases, which differ in processing function calcium through kidneys. However, it is still difficult to distinguish between the two diseases due to their significant overlaps in ranges on these indicators. The *CaSR* gene has numerous mutations linked to FHH, and it is becoming more widely known that the CaSR has a wide range of functional variability. Authors further described that the commonly used biochemical test to distinguish between pHPT and FHH is the calcium: creatinine clearance ratio. A precise diagnosis of FHH requires genetic testing, as this test is still constrained by an extensive uncertain range (11).

Hinnie *et al.* described that normal biochemical findings in FHH are comparable to those in mild pHPT, which is mild hypercalcemia with an abnormally high PTH. This can cause FHH to be misdiagnosed as pHPT or sometimes lead to a parathyroidectomy that is not necessary. Even the most advanced biochemical estimates of serum or urine are not efficient to distinguish between FHH and pHPT. In terms of biomarkers including serum calcium, chloride, magnesium, and PTH there is a striking resemblance between these two conditions (12). Similarly, Vargas-Poussou *et al.* observed a considerable phenotypic overlap among FHH and pHPT patients making it challenging to distinguish between the two groups using only laboratory data (13). Christensen *et al.* suggested a two-step process for diagnosis which can further help in reducing the chances of misdiagnosis or unneeded intervention. First, a 24-hour urine sample is used to measure the ratio of calcium to creatinine clearance. Second, the *CaSR* gene is checked for changes in all patients with a calcium/creatinine clearance ratio of 0.020 or less. This approach is 98% accurate as a diagnostic tool (6). Similarly, in our patient, calcium/creatinine clearance was determined prior to genetic testing. Generally, FHH1 and FHH2 have comparable clinical presentations. Patients with FHH who exhibit significant hypermagnesemia, cognitive decline, and low bone mineral density should have their *AP2S1* gene mutated (14).

Heterozygous CaSR mutations are the underlying cause of FHH type 1, which has a generally benign course (15). The clinical heterogeneity of heterozygous CaSR mutants has been increasingly proven, despite the fact that the mutations typically result in asymptomatic FHH (16). Whereas serious neonatal hyperparathyroidism is a potentially fatal condition that can arise from homozygous inactivating mutations of CaSR, which are significantly less common. It is linked to a significant percentage of CaSR mutations that affect the Ca^{2+}-binding sites, especially at the main Ca^{2+} binding site, the Venus flytrap domain (VFTD) cleft. Hyperplasia, typically seen in the four glands in neonatal hyperparathyroidism, is mainly triggered by mutant sensors in the plasma membrane. The most common mutations associated with this condition are heterozygous or compound homozygous inactivating variants of CaSR, or occasionally only *de novo* heterozygotes, like the R185Q and R227Q mutations, which change the MAP-kinase pathway (17).

Grant *et al.* narrated that mutations in FHH/neonatal

severe hyperparathyroidism (NSHPT) can decrease CaSR trafficking to the plasma membrane. A new steady state level of plasma membrane CaSR is created by agonist driven anterograde CaSR trafficking, which amplifies CaSR signaling. This level of CaSR is maintained with little functional desensitization as long as extracellular Ca^{2+} is elevated. When external Ca^{2+} is raised, restoration of FHH/NSHPT mutants necessitates a steady-state intracellular Ca^{2+} response (18). While Wang *et al.* explained in animal model-based study the phenomena of difference in severity of both forms of FHH as they reported that in HEK293 cells, the exon 5-deleted mutant CaSR, which when homozygously expressed causes NSHPT in mice, lacked functional cell surface expression and the ability to sense [Ca^{2+}] change. Heterodimerization with wild-type (WT) CaSR effectively restored mutant CaSR trafficking to the cell surface. Comparing CaSR/mCaSR heterodimers to WT CaSR homodimers, they demonstrated lower affinity and comparable effectiveness. The overall reduction in WT/mutant CaSR heterodimer affinity and cell surface expression leads to a decrease in the CaSR signaling responsible for FHH1 (15).

Jalilian *et al.* described a case of a patient with elevated calcium levels in serum and decreased urinary calcium excretion. A CaSR mutation confirmed the diagnosis of FHH. The authors further suggested that the use of genetic test results could successfully avoid unnecessary parathyroid surgery (19). Sumida *et al.* reported a case of a 16-year-old girl with FHH. Genetic testing showed that the heterozygous CaSR mutation was deleterious, allowing a clear diagnosis of FHH type 1. The genetic test for calcium sensing receptors can help differentiate between FHH and pHPT, especially in asymptomatic cases (20). Likewise, the diagnosis of FHH in our patient was confirmed after the genetic testing. Since FHH is an asymptomatic disease with no significant or serious complications, therefore, in most cases no intervention is required. Even though some research studies support the use of cinacalcet in FHH, it is not evident if it is necessary or beneficial (21). Due to the disease's rarity, our case report is limited to the presentation of a single patient. Even though there are studies highlighting the importance of genetic testing for the diagnosis of FHH in the literature, we believe it is important to report this study because it can add to the existing literature and further demonstrate the value of genetic testing for diagnosis which can assist in preventing unnecessary parathyroid surgical interventions.

Conclusions

FHH is a rare condition that needs to be distinguished from pHPT so that patients with hypercalcemia do not needlessly undergo exploratory parathyroidectomy. For differentiating pHPT from FHH, a combination of clinical suspicion, biochemical testing, and genetic analysis is performed, and the diagnosis can only be confirmed after the genetic test results.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-23-132/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-23-132/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient and her relevant family member for publication of this case report. A copy of the written consent is available for review by the editorial office of this journal.

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