Familial hypocalciuric hypercalcemia: sometimes it is not what it seems

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Summary
Familial hypocalciuric hypercalcemia (FHH) is an uncommon cause of hypercalcemia. Its prevalence is estimated to be 1:78,000 people. We describe a case with atypical presentation confirmed by genetic diagnosis. This is a case of a woman of 74 years of age with osteoporosis referred to the endocrinology service with suspected primary hyperparathyroidism (HPTP). She presented with a high level of parathyroid hormone (96.3 pg/ml, normal limits (NL): 15-65 pg/ml), with normal levels of calcium, phosphorus and magnesium, as well as a raised level of calciuria. She subsequently presented with normal levels of PTH, raised levels of calcium, combined with normal -high calciuria. The calcium/creatinine clearance ratio (CCCR, in mmol/l) varied between 0.011 and 0.02 mmol/l. A CCCR <0.01 is suggestive of FHH, and a CCCR >0.02, of HPTP. This ratio is within the range between 0.01 and 0.02 mmol/l, a reason which justifies requesting a genetic test in all patients with normal or high PTH, hypercalcemia and CCCR <0.02, requirements which our index case meets.

Keywords: familial hypocalciuric hypercalcemia, primary hyperparathyroidism, CaSR, calcium/creatinine clearance ratio (CCCR).
Introduction

Hypercalcemia is a common finding in clinical practice. Among the different causes are primary hyperparathyroidism (PHPT) and tumour-induced hypercalcemia, which represent more than 90% cases, but there are also others such as vitamin D intoxication, granulomatous diseases, drugs such as thiazides and lithium, hyperthyroidism and familial hypocalciuric hypercalcemia (FHH). This last condition represents a benign cause of dominant autosomal hereditary hypercalcemia which does not usually require treatment. In most cases FHH is the result of mutations which inactivate the calcium sensing receptor (CaSR)1. Its prevalence is estimated as being 1:78,000 persons2, but it is assumed that it must be higher since there are many cases which are not detected. Patients usually present with light-to-moderate hypocalciuria, inappropriately normal levels of parathyroid hormone (PTH) and normal or high levels of magnesium. Below, we present a case which did not suggest initially that it must be higher since there are many cases of FHH, with compatible genetic studies. With this in mind it may help to differentiate between these two conditions, and that the genetic test to determine mutations in the CaSR is the only sure diagnostic method, even though these tests are not sensitive in 100% of cases, and that a careful evaluation of the family history may be required in order to confirm or reject the diagnosis, even with a negative result in the genetic test.

Presentation of the Case

A case of a woman of 74 years of age with type 2 diabetes, with arterial hypertension (AHT) in treatment with losartan, and with postmenopausal osteoporosis diagnosed at 68 years of age in the rheumatology clinic in treatment with alendronate weekly (bone densitometry: T-score femoral neck -1.3 SD and lumbar spine -3.9 SD). She was referred to the endocrinology clinic because in this context she presented with high PTH, with normal levels of calcium, phosphorus and magnesium, as well as a high level of calciuria (Table 1).

In this first evaluation the condition was labelled as hypercalciuria with high PTH without hypercalcemia to be studied, with the possible diagnosis of normocalcemic PHPT.

The study was widened and the bisphosphonate was stopped for 3 months before carrying out a baseline study, with successive analyses seeing normal rates of PTH with raised levels of blood calcium, phosphorus and magnesium within the normal range. At the start of the follow up she presented high calciuria which subsequently normalised without becoming low. A parathyroid gammagraphy was also carried out, which was negative. The calcium/creatinine clearance ratio (CCCR, in mmol/l) was calculated, which varied between 0.011 and 0.02, not being clearly lower than 0.01, a ratio <0.01 is suggestive of FHH and >0.02 of PHPT. CCCR is limited within the range 0.01 and 0.02, which is the situation we found in our case. This test has a sensitivity of 80% and a specificity of 88% for the diagnosis of FHH, which has resulted in the suggestion that the diagnosis should be carried out in two steps: requesting a genetic test in all patients with normal or high PTH, hypercalcaemia and CCCR <0.02, requirements with which our index case complied. Although limited in its specificity and sensibility CCCR may alert the doctor to the possible presence of FHH even with a normal 2 level of 24 hour urinary calcium secretion10.

HPP is an uncommon condition, and on occasion its clinical presentation overlaps with PHPT, which is much more common. The excretion of calcium in urine over 24 hours may be low, normal or high in both pathologies, which means that the diagnosis can be confused. It should be taken into account that CCCR may help to differentiate between the two conditions, and that the genetic test to determine mutations in the CaSR is the only sure diagnostic method, even though these tests are not sensitive in 100% of cases, and that a careful evaluation of the family history may be required in order to confirm or reject the diagnosis, even with a negative result in the genetic test.

PHPT and FFH. A ratio <0.01 is suggestive of FHH and >0.02 of PHPT. CCCR is limited within the range 0.01 and 0.02, which is the situation we found in our case. This test has a sensitivity of 80% and a specificity of 88% for the diagnosis of FHH, which has resulted in the suggestion that the diagnosis should be carried out in two steps: requesting a genetic test in all patients with normal or high PTH, hypercalcaemia and CCCR <0.02, requirements with which our index case complied. Although limited in its specificity and sensibility CCCR may alert the doctor to the possible presence of FHH even with a normal 2 level of 24 hour urinary calcium secretion10.

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The patient studied presented this alteration heterozygously".

In approximately 65% of cases FHH is the result of an inactive mutation in CaSR, whose genes reside in the long arm of chromosome 3 (3q21.1). This form of FHH is called FHH 11, and is the form present in our patient. FHH2 derives from inactive mutations of the protein G alpha 11 (19p): a guanine-binding protein which bonds with CaSR to activate the phospholipase C, which contributes to the inhibition of the release of PTH when the concentrations of extracellular calcium are raised. Lastly, FHH3 is linked with mutations in AP2S1 (19q13).

To date, around 200 mutations in CaSR associated with FHH have been described (http://www.casrdb.mcgill.ca). In addition, there is evidence that the biochemical severity of the FHH is specific to the mutation12, and hence the heterogeneity of the FHH genotypes result in different phenotypes, above all with respect to the calciuria. While hypocalciuria is the classic finding of FHH, hypercalciuria has been seen in families with a confirmed genotype of FHH. In FHH, hypercalcaemia does not usually have clinical consequences, but there are cases described in which it has been associated with pancreatitis, chondrocalcinosis, nephrolithiasis, and other symptoms associated with PHPT13.

The clinical guides recognise CCCR as the biochemical index of choice to differentiate between PHPT and FFH. A ratio <0.01 is suggestive of FHH and >0.02 of PHPT. CCCR is limited within the range 0.01 and 0.02, which is the situation we found in our case. This test has a sensitivity of 80% and a specificity of 88% for the diagnosis of FHH, which has resulted in the suggestion that the diagnosis should be carried out in two steps: requesting a genetic test in all patients with normal or high PTH, hypercalcaemia and CCCR <0.02, requirements with which our index case complied. Although limited in its specificity and sensibility CCCR may alert the doctor to the possible presence of FHH even with a normal 2 level of 24 hour urinary calcium secretion10.

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Table 1. Changes in biochemical parameters during follow-up

<table>
<thead>
<tr>
<th></th>
<th>Creatinine</th>
<th>Total calcium</th>
<th>PTH</th>
<th>Calciuria</th>
<th>CCCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal limits</td>
<td>0.5-1.2 mg/dl</td>
<td>8.5-10.5 mg/dl</td>
<td>15-65 pg/ml</td>
<td>50-250 mg</td>
<td>*mmol/l</td>
</tr>
<tr>
<td>Initial assessment (1st visit)</td>
<td>0.6</td>
<td>10.4</td>
<td>96.3</td>
<td>483.2</td>
<td>0.014</td>
</tr>
<tr>
<td>3 months without bisphosphonate (2nd visit)</td>
<td>0.7</td>
<td>11.2</td>
<td>61</td>
<td>474.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Subsequent consultations</td>
<td>0.6±0.08</td>
<td>10.7±0.3</td>
<td>48.5±12</td>
<td>213±93</td>
<td>0.014±0.003</td>
</tr>
</tbody>
</table>

* CCCR: clearance calcium/creatinine clearance: (Calcium urine x Creatinine plasma)/(Calcium plasma x Creatinine urine); * Values expressed as mean ± SD according to the reviews in the 2 years later.
* Not included in the table the values of magnesium (Mg) and phosphorus (P) plasma, and that at all times remained within normal limits (Mg: 1.7-2.5 mg/dl y P: 2.5-4.5 mg/dl).

In conclusion, it should be borne in mind that, when presented with slight hypercalcemia doctors should think of the possibility that they are dealing with FIH, because, in spite of its name, hypercalcemia may be neither familial nor hypocalciuric. CCCR, combined with genetic tests may help us avoid erroneous diagnoses and unnecessary surgery for the patient.

**Bibliography**