FAMILIAL HYPOCALCIURIC HYPERCALCEMIA – CASE REPORT

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INTRODUCTION

Familial Hypocalciuric Hypercalcemia (FHH) is a rare genetically heterogeneous disorder with 3 known variants, all present with autosomal dominant inheritance.

An inactivating mutation of calcium sensor receptor (CaSR) is the cause of subtype 1, which results in general hyporesponsivity to calcium and represents 65% of FHH cases. Subtype 2 is due to an inactivating mutation in a1 subunit of G protein that is involved in the signaling cascade of CaSR. It was identified in >10% of patients with FHH in whom subtype 1 and 3 had been excluded. Type 3 FHH, or Oklahoma variant, results from a mutation in the sigma subunit of AP2 (Adaptor protein), a protein with an important role in the endocytosis process of CaSR. It occurs in >20% of FHH patients without mutation in CaSR.

FHH is characterized by hypercalcemia and relative hypocalciuria, with inappropriately normal or elevated PTH. It is generally asymptomatic and no treatment is needed.

The differential diagnosis with Primary Hyperparathyroidism (PHPT) is essential and it is based on the calculation of Calcium-Creatinine Clearance Ratio (CCCR), which, when under 0.02, points to the diagnosis of FHH. Genetic test is necessary for confirmation.

CASE REPORT

S.V.C., Female, caucasian, 16 years-old (yo)

Referred to ENDOCRINOLOGY for:

Hypercalcemia found in routine analysis

Ca 11.5 mg/dl (nv 8.8-10.4)

Previous Medical History:

Unremarkable

Family History:

- Mother died at 39 yo from hepatocellular carcinoma
- Maternal aunt died at 33 yo from sarcoma
- Maternal cousin died at 18 yo from ovarian carcinoma

EVALUATION:

- Clinical: asymptomatic
- Physical Examination: Normal
- Thyroid/Parathyroid Ultrasound (US):
  - Thyroid gland with normal size, rough echostructure, without nodules. No alterations in parathyroid.
- Tc-Sestamibi Parathyroid Scan:
  - Normal
- LABORATORIAL: 28/2/05 12/9/05
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<th>Phosphorus mg/dl</th>
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No alterations:

Renal/Abdominal US

Thorax X-ray

Routine Analysis

CBC, SV, kidney and hepatic function, proteinogram - normal

RELATIVES EVALUATION

- Serum Ca and PTH in S.V.C.’s father and paternal half-brother were normal.

H.M.V.H., Female, caucasian, 64 yo, S.V.C. maternal grandmother

Referred to ENDOCRINOLOGY for:

Multinodular Goiter

LABORATORIAL: 19/03/08 01/12/10

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DNA sequencing of CaSR gene revealed a novel frameshift mutation in heterozygote in III.1 and III.2.

Deletion of G residue in codon 649 of exon 7 produces a premature stop in codon 697

This mutation is predicted to result in a truncated form of CaSR receptor and is the probable cause of FHH.

The receptor encoded by the mutant allele is not expected to be expressed at the cell surface and therefore, it will not interact, in a dominant negative manner, with the wild-type CaSR present on the cell membrane, thus explaining the modest effect on plasma calcium values, and the typical asymptomatic FHH observed in the heterozygotes.

CONCLUSIONS

FHH is a rare benign condition, that must be considered in the differential diagnosis of hypercalcemia with normal or elevated PTH. CCCR is recognized as adequate to distinguish FHH from PHPT. However, there is a range of values from which the test is not safe and the definitive diagnosis of FHH requires genetic confirmation, saving this patients from unnecessary surgeries. In this case report, we stand out the identification of a mutation in CaSR not previously described in the literature.