Autosomal dominant hypocalcaemia: A novel mutation

Hipocalcemia autosómica dominante: una nueva mutación

Dear Editor:

We present the finding of a new activating mutation of the calcium-sensing receptor (CaSR) gene. The mutation was identified in 2 subjects from the same family; they had asymptomatic chronic hypocalcemia with low parathyroid hormone (PTH) and inappropriate urinary calcium excretion.

The CaSR is primarily expressed in the parathyroid glands and the kidney. It is controlled by extracellular calcium, and allows for the regulation of PTH secretion and the tubular reabsorption of calcium, depending on changes in extracellular calcium levels. Genetic changes in the CaSR may cause changes in calcium homeostasis. Both activating and inactivating changes in calcium metabolism caused by mutations have been reported. One third of patients with idiopathic congenital hypoparathyroidism may have activating CaSR mutations. This results in autosomal dominant hypocalcaemia (ADH) that may present a broad range of clinical manifestations. Over 50 mutations causing ADH have been identified to date. ADH is characterized by hypocalcemia, detectable but inappropriately low PTH, and high calcium, considering the hypocalcemia. Many of these patients, particularly those with no symptoms, are underdiagnosed or diagnosed with idiopathic hypoparathyroidism. Treatment with calcium or vitamin D supplements may exacerbate hypercalcuria, causing nephrocalcinosis, stones, and renal failure.

We report the case of a 25-year-old woman, referred to our clinic for hypocalcemia detected as an incidental finding in routine pregnancy check-ups 2 years previously. According to the patient, the diagnosis had not been investigated further and no treatment was started as she had no symptoms.

Low calcium levels were confirmed (7.76 mg/dL; normal range: 8.6–10), together with PTH levels in the low normal range (20 pg/mL; normal range: 15–65); the urinary calcium level was 34.3 mg/24 h (normal: 0–300). On further investigation into her family history, a similar pattern of hypocalcemia with low PTH levels was found in her father. Both patients were found to have normal 25- and 1,25-vitamin D levels, and treatment with oral calcium caused increased urinary calcium levels in both, with no significant changes in either serum calcium or PTH levels.

A genetic test was proposed to the patient and her father. After obtaining their informed consent, the CaSR gene was studied. A missense mutation was found in exon 7: c.2621G>T (p.Cys874Phe). This mutation was assessed using biocomputing applications (MutationTaster and PolyPhen-2) and was considered pathogenic.

The father was referred for monitoring to his reference hospital. We completed the study of our patient with a nephrourological ultrasound, which revealed no
abnormalities. No calcifications in basal ganglia were found in computed tomography (CT) of the head. Bone densitometry showed osteopenia in the femoral head with a T-score of −1.1.

The patient was advised to avoid treatments with calcium or vitamin D due to possible adverse effects, given the absence of symptoms.

Given the family history and genetic findings, it was decided to study the patient’s son. The calcium and PTH levels detected were in the normal range (9.82 and 22.6 pg/mL respectively). The genetic study showed that he was not a carrier of the mutation identified in the family.

We report a novel mutation in the CaSR gene in two family members with asymptomatic hypocalcemia. Biochemical findings support the diagnosis of ADH, and confirm the pathogenic role of the mutation. Virtually every family with ADH has its own mutation. They are often heterozygous missense mutations.

A finding of hypocalcemia not associated with undetectable or greatly decreased PTH suggests a diagnosis of hypocalcicuric hypercalcemia.1

There is a clear consensus against routinely treating asymptomatic patients. Treatment should be reserved for patients with clinically evident hypocalcemia. In these cases, calcium supplements and/or oral vitamin D should be administered at the lowest possible dose. The goal is to maintain the lowest serum calcium level that allows for symptom control.

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References


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Pituitary adenoma associated with pheochromocytoma/paraganglioma: A new form of multiple endocrine neoplasia a–c

Adenoma hipofisario asociado a feocromocitoma/paraganglioma: una nueva forma de neoplasia endocrina múltiple

Dear Editor:

Multiple endocrine neoplasia (MEN) syndromes are characterized by the presence of tumors affecting two or more endocrine glands. Pituitary adenoma (PA) and pheochromocytoma/paraganglioma (Pheo/PGL) are common tumors in MEN type 1 and 2 respectively. The presence of both tumors in a patient is exceptional and was first reported by Iversen in 1952.1 Advances in genetics have suggested a possible common pathogenetic mechanism in which mutations of genes encoding the enzyme succinate dehydrogenase (SDH) could be involved.2,3 In 2015, Xekouki et al. confirmed the existence of this association called “the three P association” or 3Ps: pituitary adenoma with pheochromocytoma/paraganglioma.4 Three cases of this association, one of them partially described previously, are reported below.5

Case 1

This was a 54-year-old male with no remarkable family history and with high blood pressure. Bilateral adrenal