CASE REPORT

Association of parathyroid adenoma and familial hypocalciuric hypercalcaemia in a teenager

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Abstract

Objective: Familial hypocalciuric hypercalcaemia (FHH) is clinically characterized by mild to moderate parathyroid hormone (PTH)-dependent hypercalcaemia, autosomal dominant pattern of inheritance, and normal to frankly reduced urinary calcium excretion in spite of a high serum calcium (clearance (Ca)/clearance (Cr) < 0.01). FHH has a benign course and should be differentiated from primary hyperparathyroidism. It is usually caused by a heterozygous loss-of-function mutation in the calcium-sensing receptor gene (CASR).

Design: We report the case of a 16-year-old patient with hypercalcaemia and a mixed family history of parathyroid adenoma and mild hypercalcaemia. Serum calcium was 14 mg/dl with a serum iPTH of 253 pg/ml.

Results: A neck 99mTc-sesta MIBI tomoscintigraphy showed a definite hyperactivity in the left upper quadrant. A surgical four-gland exploration confirmed a single parathyroid adenoma. After surgical resection of a left superior parathyroid adenoma, the patient's hypercalcemia improved but did not normalize, returning to a level typical of FHH. An inactivating mutation in exon 4 of the CASR gene, predicting a p.Glu297Lys amino acid substitution was found.

Conclusions: Thus, this 16-year old patient presented with the association of FHH and a single parathyroid adenoma. The young age of the patient and the association of parathyroid adenoma and FHH in his grandmother argue for a causal link between CASR mutation and parathyroid adenoma in this family. This case contributes to illustrate the expanding clinical spectrum of CASR loss-of-function mutations.

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Introduction

Familial hypocalciuric hypercalcaemia (FHH) is clinically characterized by mild to moderate parathyroid hormone (PTH)-dependent hypercalcaemia (unpressed PTH), autosomal dominant pattern of inheritance, and normal to frankly reduced urinary calcium excretion in spite of the coexistent hypercalcaemia (clearance (Ca)/clearance (Cr) < 0.01). FHH is usually caused by a heterozygous loss-of-function mutation in the calcium-sensing receptor gene (CASR). The pathological examination of parathyroid glands in patients with FHH who have undergone neck surgery shows that enlarged glands and mild parathyroid hyperplasia can occur but that nodularity or adenoma is not a usual finding (1, 2).

FHH has a benign course and parathyroidectomy should not be carried out in FHH as it does not cure hypercalcaemia.

In the last few years, families with heterozygous loss-of-function mutation of CASR have been reported with mixed clinical pictures of FHH and frank hyperparathyroidism (HPT) features such as hypercalciuria, kidney stones, and multiglandular parathyroid hyperplasia (3–5). Another rare clinical presentation of patients with heterozygous loss-of-function mutation of CASR is the occurrence of an isolated parathyroid adenoma along with FHH. To our knowledge, this has been reported once in a middle aged woman (6).

We report the case of a 16-year-old boy with the association of FHH and a single parathyroid adenoma.

Because primary HPT is a common endocrine disease, it is expected to occur in kindreds with FHH, as well as in those without. Nevertheless, the patient reported here presents with primary HPT at an unusually young age and his grandmother has the same clinical presentation, although later in life. The clustering of FHH and parathyroid adenoma in this family might thus not be a coincidence.

Methods

Calcium, phosphorus, and creatinine were measured by automated laboratory methods. The urinary calcium and creatinine measurements were done on spot urine samples for practical reasons. Spot urine Ca/Cr measurements have been shown to correlate well with...
24-h urine calcium excretion (7) and are much less error prone to collect than a 24-h specimen. Seven pre-operative and four post-operative spot urine samples were obtained from the described patient and the calcium and creatinine measurements were extremely similar in these different spot samples.

Calcium/creatinine clearance ratio (CCCR) was calculated as:

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\text{CCCR} = \frac{\text{spot-U-calcium/P-calcium, total}}{\text{spot-U-creatinine/P-creatinine}}.
\]

iPTH was determined by an immunometric assay (ADVIA Centaur, Siemans Healthcare, Munich, Germany; reference values 10–95 pg/ml). Serum 25(OH) cholecalciferol was measured by competition immunoassay (LIAISON, DiaSorin, Stillwater, MN, USA; reference values: 12–30 ng/ml). Neck \(^{99m}\text{Tc}\)-sesta MIBI tomoscintigraphy was performed 30 min after i.v. injection of 740 MBq of \(^{99m}\text{Tc}\)-sesta MIBI.

Informed consent was obtained from the patient and his father and grandmother for the DNA study. DNA was extracted from EDTA blood. PCR amplification and DNA sequencing of the six coding exons and parts of the flanking introns of the \(\text{CASR}\) have been carried out as described by Pearce et al. (8).

**Case report**

A 16-year-old male patient presented with abdominal pain, fatigue, and intermittent polyuria and polydipsia. He was born from distantly related Turkish parents. His personal history was unremarkable. His family history revealed hypercalcaemia in both his father and paternal grandmother. The paternal grandmother had a parathyroid adenoma surgically removed at 55 years of age. Her pre-operative serum calcium had reached 13 mg/dl. She underwent a surgical 4-gland exploration: a left lower parathyroid adenoma was found and excised. The macroscopic appearance of the other three parathyroid glands was normal according to the experienced surgeon. The pathological examination confirmed a \(1 \times 0.6 \times 0.5 \text{ cm}\) parathyroid adenoma.

Physical examination of the boy was unremarkable: weight 51.7 kg, height 177 cm (0.5 SDS), body mass index 16.1 kg/m\(^2\) (–2.5 SDS), Tanner pubertal stage A3P5G5, blood pressure 95/58 mmHg, and pulse rate 62/min.

Laboratory results are shown in Table 1. Serum calcium level was high, serum phosphorus was normal, PTH was markedly increased, and calciuria was low. Prolactin, gastrin, serum amylase, calcitonin, and thyroid function, were normal. Serum 25-hydroxyvitamin D (25OHD) was low.

A screening of the serum calcium level was performed in the adult family members of the index case: the father, two siblings out of three, and the paternal grandmother had mild hypercalcaemia, unsuppressed serum PTH, and marked hypocaliuria (Table 1).

A mutation in exon 4 of the \(\text{CASR}\) gene was found, predicting a p.Glu297Lys amino acid substitution in
the patient, his father and his paternal grandmother. This inactivating mutation is expected to alter the N-terminal extracellular domain of the receptor involved in calcium binding and has been described in heterozygous patients with FHH and homozygous patients with neonatal severe HPT (9, 10).

During a 6-months follow-up period, hypercalcaemia worsened along with complaints of fatigue, polyuria, and polydipsia. Hypocalciuria persisted and serum iPTH remained markedly elevated. A neck echography was normal. The $^{99m}$Tc-sesta MIBI tomoscintigraphy showed a significantly increased tracer uptake in the region corresponding to the left upper parathyroid gland. Renal echography and jaw X-ray were normal. The sequencing of exons 2–9 of the MEN1 gene was normal.

A surgical 4-gland exploration was carried out: a left upper parathyroid adenoma was found and excised. The pathological examination confirmed a 474 mg and $1.4 \times 1 \times 0.5$ cm parathyroid adenoma. The macroscopic appearance of the other three parathyroid glands was normal according to the experienced surgeon. The surgeon did not biopsy the three other parathyroid glands.

During post-operative follow-up (one year; Table 1) the serum calcium level remained slightly elevated with marked hypocalciuria, upper-normal, unsuppressed PTH, and a low serum 25OHD.

**Discussion**

We report the case of a teenager with both FHH and a parathyroid adenoma with a family history of FHH and parathyroid adenoma.

The markedly elevated serum calcium, iPTH, and neck $^{99m}$Tc-sesta MIBI tomoscintigraphy suggested the presence of a parathyroid adenoma and led to a surgical 4-gland exploration. Tomoscintigraphic localization was correct and a single parathyroid adenoma was found and excised.

The post-operative mild to moderate PTH-dependent hypercalcaemia, autosomal dominant pattern of inheritance, frankly reduced urinary calcium excretion in spite of the coexistent hypercalcaemia and upper-normal serum magnesium pointed towards the diagnosis of FHH. This was confirmed by the detection of a heterozygous p.Glu297Lys amino acid substitution of the CASR gene.

The patient’s paternal grandmother, who shared the germline missense E297K mutation in the CASR gene and had primary HPT corrected by surgery at age 55.

 Syndromes with familial isolated HPT (FIH) include MEN1, MEN2A, the HPT-jaw tumor syndrome, and FHH. MEN1 gene sequencing was normal. MEN2A was not sequenced because the higher penetrance of medullary thyroid carcinoma and pheochromocytoma than that of HPT dominates the clinical presentation in families with MEN2A.

It is not uncommon that a patient with unrecognized FHH undergoes parathyroid surgery with the removal of a minimally enlarged parathyroid gland that may be scored as adenoma. Given that both the boy and his grandmother had a very elevated pre-operative serum calcium level (14 and 13 mg/dl respectively) and had a 4-gland exploration by an experimented surgeon that showed three other parathyroid glands of normal macroscopic appearance, we tend to believe that a true adenoma was present in both the patient and his grandmother.

The patient and his family were vitamin D deficient. Vitamin D deficiency is associated with low urinary calcium excretion. It is likely that vitamin D deficiency by reducing urinary calcium excretion may contribute to ambiguity in distinguishing primary HPT from FHH.

Vitamin D deficiency might have had a role in the development of a parathyroid adenoma in this boy. Vitamin D deficiency is more common among patients with primary HPT than among controls. Some investigators have suggested that chronic vitamin D deficiency may accelerate parathyroid adenoma growth and PTH secretion (11–13). Others have recently shown that vitamin D deficiency increases PTH secretion activity without demonstrable effect on adenoma growth (14, 15). Our patient certainly had low serum 25OHD and this could have favored the adenoma development.

The two main reports of pathological examination of parathyroid glands in FHH show slightly conflicting results: Thorgerisson et al. report one or more enlarged glands and mild parathyroid hyperplasia as a feature in most patients with FHH who had undergone neck surgery; Law et al. report 15–20% of parathyroid glands exceeding normal size in FHH, most being indistinguishable from normal by size, weight, and microscopic appearance (1, 2). Hence, parathyroid hyperplasia can occur in FHH but not nodularity or adenoma.

In recent years, the clinical spectrum of loss-of-function mutations of the CASR has expanded with the report of clinical pictures overlapping between FHH and FIH (FIHP). Carling et al. reported a family with a heterozygous inactivating mutation of the intracellular domain of the CaR associated with hypercalcaemia, unsuppressed serum iPTH, hypercalciuria, and renal calculi (3). Of note, this family, although harboring an inactivating CASR mutation, is not described as having FHH because of hypercalciuria. Parathyroid surgery was undergone by seventeen family members. The parathyroid histopathology of the family varied from mild enlargement with diffuse hyperplasia to nodule formations and microscopic findings incorrectly interpreted as single adenoma (16). The enlarged parathyroid glands of this family are monoclonal tumors as they display frequent allelic loss. The authors hypothesize that the monoclonal parathyroid lesions of this family may develop secondary to deletion of novel parathyroid tumor suppressor genes and that the germline mutation in CASR may promote parathyroid cell proliferation and susceptibility to additional potential specific genetic hits (17). Simonds et al. studied 33 kindreds with FIHP and
found CASR inactivating mutations in five kindreds. In three of these kindreds, there was hypercalcemia and in the two others, there were nephrolithiasis cases. Two probands had elevated PTH (167–179 pg/ml; N 10–65 pg/ml), diffusely enlarged parathyroid glands (3–3.5 glands excised), hypercalcemia (Ca 10.8 to 12.4 mg/dl and iPTH from 54 to 126 pg/ml). All of them underwent parathyroid surgery and had multiglandular involvement (3–4 glands removed, total weight 362–900 mg mild hyperparathyroidism: unexpected results and their implications. Journal of Clinical Endocrinology and Metabolism 2000 85 2042–2047.


