CASE REPORT

Familial isolated parathyroid adenoma in a consanguineous family

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ABSTRACT. The 23-year-old Caucasian male propositus presented with symptomatic hypercalcemia, hypophosphatemia and normocalciuria for 2 months. His 29-year-old brother had undergone an operation for recurrent parathyroid adenoma at age 26 and 28. No other member of the family was affected. His father and mother were second-degree relatives. Laboratory studies showed primary hyperparathyroidism (pHPT), while the remaining endocrine studies and genetic testing for multiple endocrine neoplasia 1 and 2A were normal. Technetium-cardiolite scintigraphy and ultrasound scans revealed a parathyroid mass at the left lower neck. Apart from bilateral hearing loss due to gentamicin treatment as a pre-term child, the patient was in of good health. Signs or symptoms of other endocrinopathies were absent. The patient was referred for parathyroidectomy with subsequent autotransplantation of the remaining glands into his sternocleidomastoid muscle. Histological examination revealed an adenoma with oncocytic differentiation, similar to that seen in his brother. The disease may follow a recessive mode of inheritance or may be due to a dominant germ-cell mutation in one of the parents. The presented case may ultimately help in elucidating the molecular genetic basis of this rare form of pHPT.

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INTRODUCTION

Primary hyperparathyroidism (pHPT) most commonly occurs sporadically with a frequency of 1:1000 in the general population (1, 2). Sporadic parathyroid adenomas appear to be of monoclonal origin. In 5% of the adenomas an over-activation of the PRAD1/cyclin D1 gene may be seen (3). Loss of tumor heterozygosity (LOH) studies have, furthermore, suggested the involvement of multiple chromosomal regions including 1q, 3q, 6q, 9p, 15q in the pathogenesis (4). Somatic mutations in the MENIN gene may be involved in a subset of spontaneous parathyroid adenomas (5, 6), while no evidence was found for an association with mutations in the calcium-sensing receptor gene (7). The retinoblastoma tumor suppressor gene appears to be inactivated in 85% of sporadic parathyroid carcinoma (8).

Approximately 10% of the patients with pHPT have a hereditary form of parathyroid adenoma (1, 2), either as part of multiple endocrine neoplasia (MEN) type 1 or type 2A, hereditary HPT-jaw tumor syndrome (HPT-JT) or as solitary endocrinopathy, which has been referred to as familial isolated pHPT.

MEN 1 is an autosomal dominant disorder associated with tumors of the parathyroid, anterior pituitary and pancreatic islets cells caused by an inactivating mutation of the MENIN gene on chromosome 11q13 (9, 10). MEN 2A is an autosomal dominant disorder characterized by medullary thyroid carcinoma, pheochromocytoma and parathyroid tumors caused by mutations in the RET oncogene on chromosome 10q11 (11). The gene causing the autosomal dominant HPT-JT has been mapped to chromosome 1q21-q32 (12). This syndrome is characterized by parathyroid tumors, fibro-osseous jaw tumors and Wilm's tumors. Familial isolated pHPT as a distinct disorder has long been subject to de-

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bate, since several kindreds had subsequently to be reclassified as MEN 1 or familial benign hypercalcemic hypocalciuria (FBHH). An autosomal dominant mode of inheritance has been reported for familial isolated pHPT and linkage has recently been proposed to chromosome 1q22-1q31 in a Portuguese kindred (13, 14). A single family with autosomal recessive inheritance of pHPT was described by Law *et al*. (15). Data on linkage to chromosome 11q13 have been controversial (16-18), but MENIN gene mutations have recently been excluded in 5 kindreds with familial pHPT (6). FBHH, finally, is a non-neoplastic functional disorder of the parathyroid glands and may be caused by heterozygous loss-of function mutations in the calcium sensor (chromosome 3q13.3-q21) or by mutations in at least two other unknown genes on chromosome 3 and 19 (19).

We here report the case of two brothers with familial isolated pHPT in a consanguineous family. The disease may follow a recessive mode of inheritance or may be due to a dominant germ-cell mutation.

MATERIALS AND METHODS

Patients

The propositus (P1) (Fig. 1), a 23-yr-old male bookkeeper, presented with a history of malaise, recurrent headaches and facial flush for two months. His general practitioner had determined a serum calcium level of 3.5 mmol/l and referred him to our outpatient clinic for further evaluation of hypercalcemia. The patient had a history of bilateral hearing loss due to damage of the inner ear after gentamicin treatment as a 3-month pre-term child and was wearing hearing aids. He had had an operation for inguinal hernia. At presentation, he was otherwise in good health, intestinal problems were absent. He had formed stools regularly once daily, no palpitations or hypertension, no evidence of galactorrhea or Whipple's triad, no history of seizures or impairment of sight. His libido and sexual life were normal. Upon physical examination, we saw a 65 kg, 175 cm athletic patient, with masculine hairtype, acne on his arms and back, but no other skin abnormalities. We found no evidence for lymphadenopathy, his thyroid gland was of normal size, lacking apparent masses. His blood pressure was 130/80 mmHg, his heart rate 64 beats/min, lung, heart and abdomen revealed no abnormalities, the neurological exam showed normal visual fields and intact cranial nerve function, except for bilateral hearing loss. Deep tendon reflexes were of intermediate level, pathological reflexes were absent.

His brother (P2) (Fig. 1), a 29-yr-old flight attendant, had had two parathyroid glands removed at the age 26 and 28 after developing symptomatic hyperparathyroidism. Both glands contained a parathyroid adenoma with oncocytic differentiation and concurrent chief cell hyperplasia. He had received previous attention for moderate hypertension with a systolic blood pressure of approximately 150 mmHg, but was not taking any medication. His current health was otherwise unremarkable, he specifically had no signs of galactorrhea, Whipple's triad or flush. Upon examination, he had a blood pressure of 180/80 mmHg. Furthermore, a group of pale, needle-head size, maculous, non-pruritic skin affections was noted on his upper abdomen. The remaining physical exam of his lung, heart, abdomen and the nervous system revealed no abnormalities.

The patient's mother and father were second-degree relatives. As depicted in Figure 1, members of the family had a history of diabetes mellitus, ulcerative colitis, hypertension, prostate carcinoma and adenoma, oligodendroglioma of the brain, and otosclerosis. There was no pHPT in the family.

Laboratory tests

Chemical and endocrine parameters were determined according to standard procedures (Table 1 and 2). For the family examination, informed written consent of each member was obtained.

Genetic analysis of the RET and MENIN gene was performed as previously described (20, 21). In brief, genomic DNA was isolated from blood leukocytes, exons 10, 11, 13-16 of the RET protooncogene and all exons of the MENIN gene were amplified by polymerase chain reaction (PCR) and subsequently analyzed by single strand conformation polymorphism analysis (SSCP), restriction digest or sequence analy-

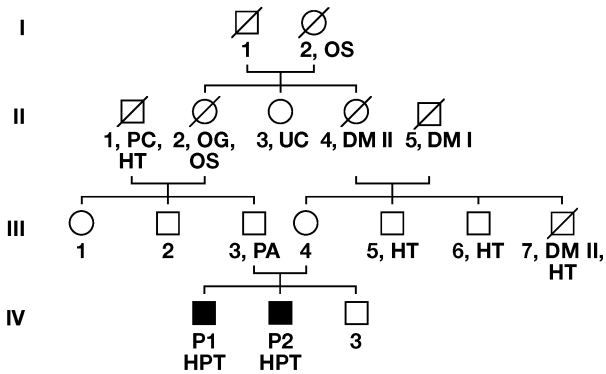

Fig. 1 - *Family tree. PC: prostate carcinoma, PA: prostate adenoma, OG: oligodendroglioma, OS: otosclerosis, UC: ulcerative colitis, HT: hypertension, DM: Type 1 or 2 diabetes mellitus*

sis. No abnormalities were detected in either gene for patient P1 or P2. Blood group analysis of III3, III4, P1 and P2 was compatible with the depicted family tree (Fig. 1).

For histological evaluation, parathyroid tissue was paraffin-embedded, sectioned and stained with hematoxyline/eosin according to standard procedures.

Clinical course and discussion

At presentation P1 suffered some of the typical symptoms of hypercalcemia (1, 2). Concurrent hypophosphatemia and elevated levels of intact parathyroid hormone (PTH) made pHPT a likely diagnosis, and a 27x15x18 mm left lower cervical mass upon ultrasound, consistent with parathyroid adenoma that enhanced technetium cardiolite (Fig. 2). After normal

Table 1 - *Laboratory findings.*

Description	P1 pre-op	P1 post-op	P2	Units of measure	Normal range
Chemistry-plasma					
Calcium	3.15	2.31-2.37	2.36-2.51	mmol/l	2.15-2.60
Ion. calcium	1.58	1.18-1.26	1.14-1.32	mmol/l	1.17-1.30
Magnesium	0.87	0.91	0.86	mmol/l	0.73-1.06
Phosphate	0.56	0.83-1.07	0.67-0.85	mmol/l	0.75-1.45
Endocrinological–serum					
Thyroxin	5.6	ND	5.3	µg/100 ml	4.5-12
Triiodothyronin	1.41	ND	1.1	ng/ml	0.45-2.0
Thyroxin binding globulin (TBG)	21.3	ND	20.7	µg/ml	12-30
T_4/TBG	0.26	ND	0.26		0.25-0.5
Calcitonin	8	0.9	2.6	pg/ml	<14
Thyreotropin	1.56	ND	1.32-1.71	µU/ml	0.3-4.0
Luteotropin	6.8	ND	6.9	U/l	1.5-14.0
Follicle stimulating hormone	11	ND	3.0	U/l	1.0-14.0
Prolactin	6.9	6.3	6.5	ng/ml	<20
Adrenocorticotropin	18	17	20-32	pg/ml	<100
Cortisol (08:00 h)	11.1	9.4	7.6-13.1	µg/100 ml	4.4-22.4
Renin	0.5	98.6	0.8-0.9	ng/ml/h	0.2-2
Aldosterone	37.9	0.9	36.2-61.2	pg/ml	<250
DHEAS	1630	ND	1535	ng/ml	11-7000
Androgens	5.9	ND	4.3	ng/ml	2.8-8.8
Free testosterone	29.41	ND	30.26	pg/ml	11.4-36.5
Epinephrine	48-108	ND	40-136	ng/l	<120
Norepinephrine	190-404	ND	195-743	ng/l	<400
Dopamine	25-50	ND	23-48	ng/l	<60
Insulin-like growth factor-1	196	193	188	ng/ml	85-169
Intact parathyroid hormone	103-108	16.2-32.4	39.7-56.7	pg/ml	10-65
Osteocalcin	45.9	7.6	15.7	ng/ml	4-20
1,25-$(OH)_2$-Vitamin D_3	nd	32.9	38.9	pg/ml	17-53
25-OH-Vitamin D_3	28.3	32.9	12.0-30.2	ng/ml	15-74
ICTP (cross links)	3.9	4.7	2.9	µg/ml	1.8-5
Gastrin	63.7	ND	63	pg/ml	<120
Insulin (BZ)	5 (76)	ND	8 (85)	mU/l (mg/dl)	<20 (60-110)
Insulin/BZ	0.07	ND	0.09	(mU/l)/(mg/dl)	<0.3
C-peptide (BZ)	1.49 (76)	ND	1.63 (85)	µg/l (mg/dl)	<3.0 (60-110)
HbA_{1c}	5.4	ND	5.0	%	4.7-5.9
Endocrinological-urine					
Free cortisol	36.4	56.1	40.3-66.4	µg/24 h	20-90
Aldosterone	8.4	5.6	4.3-9.4	µg/24 h	6-25
Epinephrine	36	20-29	10-28	µg/24 h	<16
Norepinephrine	95	48-68	28-90	µg/24 h	<40
Dopamine	511	468-722	305-758	µg/24 h	<430
C-peptide	50	ND	48	µg/24 h	30-150
5-HIES	4.3	ND	5.8	mg/24 h	<10
Mutational analysis					
RET-protooncogene	neg.	ND	neg.		neg.
MENIN-gene	neg.	ND	neg.		neg.

ND: not determined. All other serum-biochemical and hematological parameters as well as the urine electrolytes were in the normal range.

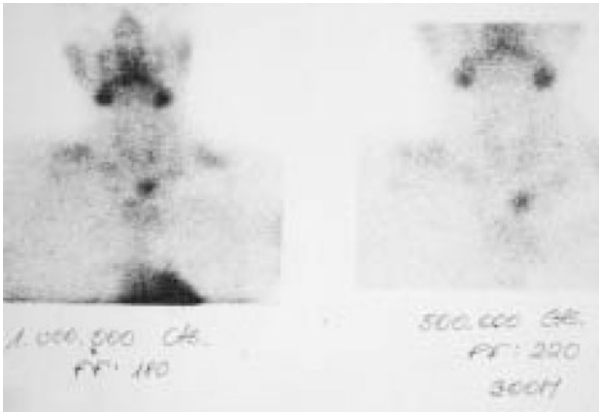

Fig. 2 - *Technetium-cardiolite scintigraphic and ultrasound studies of P1. After injection of 550 Mbq 99m-Tc-cardiolite, a pathological enhancement is seen below the thyroid on the left side of the neck, that is colocalized with a 27x15x18 mm mass found by cervical ultrasound.*

urinary excretion of calcium had been confirmed to rule out FBHH (22), the patient was referred to parathyroidectomy for treatment. Multiglandular or recurrent disease may occur in familial isolated pHPT in up to 70% and 25%, respectively (23), and was in fact seen in his older brother. Therefore, we decided to have all four parathyroid glands removed with subsequent autotransplantation of the macroscopically normal glands into his sternocleidomastoid muscle. Post-operatively, the patient recovered well and his serum PTH, calcium and phosphate levels returned to normal after a brief period of hypocalcemia that was treated with calcium tablets. The urinary calcium excretion decreased, but remained within the normal range (Table 1).

pHPT may be seen in MEN 1 and MEN 2A in 95% and 10% of the cases, respectively (24, 25). However, clinical and biochemical studies excluded presence of pituitary or pancreatic islet adenoma that often coexist in MEN 1 for both brothers. Since P1 reported headache and facial flush, and P2 had hypertension upon examination, we carefully excluded the possibility of pheochromocytoma by serial sampling of serum catecholamines and determination of the excretion of catecholamines with the urine. Both tests were not or only slightly elevated. To test for the presence of a foregut carcinoid, we examined 5-hydroxyindolacetic acid (5-HIES) in the patients' urine, which was found to be normal. The adrenal glands appeared normal in magnetic resonance studies of both patients and there was no evidence for hepatic, pancreatic or small intestinal masses. Other endocrine or renal causes of hypertension were absent. It is possible that PTH-induced hypertension may have persisted in P2 after removal of both parathyroid adenomas, as it has been observed in previous cases (2). However, the presence of idiopathic hypertension, that was seen in four members of the family, cannot be excluded.

P2 showed a group of light colored, mm-size, maculous, non-pruritic skin affections on his upper abdomen. MEN 1 is associated with angiofibromas and collagenomas (25), yet a histological confirmation of this diagnosis had not been done in the present case. The only skin affection rarely seen in MEN 2A is cutaneous lichen amyloidosis, but its appearance is different and it generally manifests with intense pruritus (26).

Screening for medullary thyroid carcinoma by ultrasound studies of the thyroid gland and determination of serum calcitonin levels in both brothers was negative as was the genetic analysis for known mutations of the MENIN gene and of the RET-proto-oncogene (27, 28). Germline mutations have not been detected in 10-20% of affected patients, and intronic or promotor changes may escape detection. However, since none of the known MEN-associated endocrine disorders had occurred elsewhere in the family, we would consider the presence of MEN 1 or 2A unlikely in this case. Furthermore, somatic mutations in the MENIN gene may be involved in a subset of spontaneous parathyroid adenomas (5, 6). However, a dominant somatic mutation in the MENIN gene would unlikely cause multiple tumors in two independent family members. Over-activation of the PRAD1/cyclin D1 gene may be seen in 5% of the adenomas (3) and LOH studies have suggested the involvement of multiple chromosomal regions including 1q, 3q, 6q, 9p, 15q in the pathogenesis (4). LOH for a tumor suppressor gene could be considered in the present case and can be consistent with recurrence in multiple parathyroid glands and in independent family members.

With a normal urinary excretion of calcium in both affected individuals, the presence of a heterozygous mutation in the calcium-sensing receptor gene causing FBHH in this family appears to be unlikely (19, 22). Furthermore, parathyroid hypercellularity may only be seen in patients with homozygous mutations of the calcium sensor, who have neonatal severe hyperparathyroidism (NSHPT) (29), while FBHH usually presents with parathyroid hypoplasia (22). The histological examination of the surgical specimens from P1 and P2 (Fig. 3), conversely, revealed parathyroid adenoma with oncocytic differentiation. Furthermore, both affected individuals were cured by parathyroidectomy, which would not be expected to be the case for individuals with FBHH. Thus, the presence of a form of FBHH in this family is unlikely.

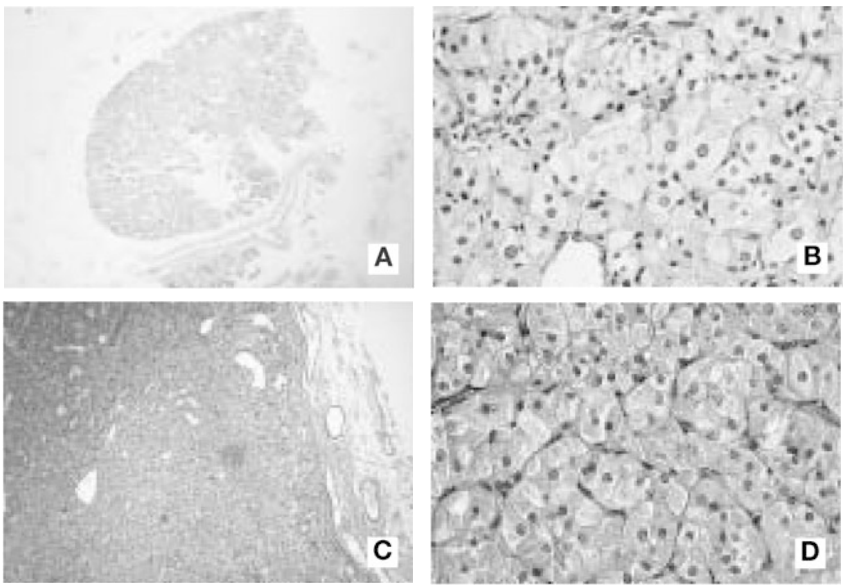

Fig. 3 - *Histological studies. A, B: normal parathyroid gland of P1 (4X and 20X magnification, respectively); C, D: parathyroid adenoma of P1 (4X and 20X magnification, respectively). Note the oncocytic differentiation of cells with hyperchromatic nuclei and abundant granular eosinophilic cytoplasm.*

Familial pHPT has been described in conjunction with fibro-osseous jaw tumors and Wilm's tumors, that occur in 44 and 33% of the cases, respectively (24). We have no clinical evidence for the presence of jaw tumors the patients' family and panoramic oral X-rays of both affected members, performed earlier in the course of orthodontic therapy, had revealed no abnormalities. The bilateral hearing loss of P1 was likely acquired in his early childhood after treatment with gentamicin and may not be part of the syndrome. Interestingly, however, his grandmother (Fig.1, I2) and great-grandmother (Fig. 1, II2) reportedly suffered deafness due to otosclerosis. However, we found only one report in the literature describing an association of sensoneurinal deafness with nephropathy and HPT (30), but no case associated with otosclerosis. The occurrence of oligodendrogliomas or prostate neoplasms in families with parathyroid adenomas has to our knowledge not been reported to date. Since the oligodendroglioma does not recur in the family and prostate neoplasm is a very common disorder, both tumors may not be part of a syndrome associated with pHPT.

We, therefore, conclude that the presented patients likely suffer from familial isolated pHPT. Existence of many genetically distinct forms of familial isolated pHPT has been suspected (24). Some had subsequently to be re-classified as MEN 1 or FBHH. Families with true solitary pHPT show adenomatous parathyroid disease or parathyroid chief cell hyperplasia, and both features were seen in the brothers presented here. Linkage to the MEN 1 or MEN 2 locus or to the PTH gene was excluded in some pedigrees with familial isolated pHPT (17, 18) and no mutations were later found in the MENIN gene (6). pHPT due to water clear cell hyperplasia was described as a separate entity with autosomal dominant inheritance strongly associated with blood group 0. This association was not seen in P1 or P2. The pedigrees of familial isolated pHPT have generally been consistent with an autosomal dominant inheritance (17), but an autosomal recessive mode has been suggested in a single case (15). As illus-

Table 2 - *Laboratory findings (family).*

Description	II3	III1	III2	III3	III4	III5	III6	P1	P2	IV3	Units of measure	Normal range
Ion. calcium	1.15	1.13	0.79	1.2	1.3	0.94	1.15	1.58*	1.14	1.21	mmol/l	1.17-1.30
Intact parathyroid hormone	44.3	29.0	61.1	39	36.4	25.2	25.2	103.8*	39.7	50.1	pg/ml	10-65

*pre-operative findings.

trated in Figure 1, the two affected brothers were born to second-degree related parents. This feature is often seen in recessive traits. However, since two individuals in only a single generation appear to be affected, the presence of a dominant germ-cell mutation in one of the parents (Fig. 1, III3) is also conceivable. Tumor development in the parathyroid glands often requires an additional event if a tumor suppressor gene is involved and LOH studies of the tumor samples of this and similar cases may help to ultimately elucidate the molecular genetic basis of this rare form of pHPT.

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