Familial isolated hyperparathyroidism due to *HRPT2* mutation☆

Hiperparatiroidismo familiar aislado asociado al gen *HRPT2*

Primary hyperparathyroidism (PHPT) is the leading cause of hypercalcemia. Although the most common presentation is sporadic PHPT attributable to a single adenoma, there are inherited forms in 10% of the cases.[1] The most common inherited variants form part of syndromes in which PHPT is associated with other endocrine disorders, including multiple endocrine neoplasia (MEN) type 1 and 2, hyperparathyroidism-jaw tumor syndrome (HPT-JT), familial hypocalciuric hypercalcemia (FHH), and familial isolated hyperparathyroidism (FIHP).

We present the cases of a family with FIHP, in which the index case (case 1) was first evaluated in 2006. Since then a total of three generations have been studied, comprising 15 family members, of which 10 are carriers of the *HRPT2* gene mutation, while 5 are symptomatic carriers. Fig. 1 describes the family tree and summarizes the main clinical, laboratory, and histological characteristics of the affected patients.

Case 1: A 20-year-old female consulted due to PHPT with nephrolithiasis and osteopenia. The MIBI scintigraphic findings proved negative on two occasions. A right inferior parathyroidectomy was performed, with intraoperative reporting of parathyroid hyperplasia. The intraoperative parathyroid hormone (PTH) levels decreased adequately according to the Miami criteria.[2] After surgery, normal PTH and calcium levels were maintained.

Case 2: A 50-year-old male presented with symptoms of nephrolithiasis. The laboratory tests revealed hypercalcemia, hypophosphatemia and inappropriate PTH elevation, with negative MIBI scintigraphy. There was no evidence of associated endocrine disorders. Surgery revealed an enlarged left superior parathyroid gland. The other glands showed no alterations. A left superior parathyroidectomy was performed, and a lowering of the PTH levels was verified intraoperatively. The histology report indicated parathyroid carcinoma. Subsequent controls proved adequate.

On identifying two members with PHPT in the same family, a molecular study was made including an analysis of the *HRPT2* gene (1q25-q31) in peripheral blood through automated sequencing, using specific DNA primers flanking the region where the mutation responsible for the disease is located in this family. This study revealed a heterozygous mutation in exon 6, c.456_459dup/p.Ala154Ile*fs*X16, in the first two cases and in the other carriers.

Case 3: A 29-year-old male presented with normocalcemic hyperparathyroidism. The MIBI scan revealed an ectopic parathyroid adenoma. A subtotal parathyroidectomy plus thymectomy was performed. The pathology report indicated parathyroid hyperplasia.

A genetic study was also made of the siblings of the father, and was found to be negative in 5 of them and positive in one (case 4).

Case 4: A 56-year-old female, currently under evaluation due to osteopenia, renal colic episodes and vitamin D deficiency. Completion of the study is pending, with subsequent surgery if required.

Case 5: A 37-year-old male presented with symptomatic PHPT associated with microlithiasis and osteopenia of the femur. A subtotal parathyroidectomy with thymectomy was recently carried out. The histology report indicated a right inferior parathyroid adenoma, with hyperplasia of the other glands. The patient has three offspring, two of whom carry the gene.

The asymptomatic carriers of the familial mutation undergo annual controls with laboratory tests and neck and kidney ultrasound explorations.

Familial isolated hyperparathyroidism is considered an autonomous non-syndromic entity or an incomplete expression of one of the genetic syndromes causing PHPT. The diagnosis is established through exclusion and requires the presence of at least two first-degree relatives with PHPT and no other endocrine manifestations[1] such as hypophyseal and pancreatic disease characteristic of MEN-1 or fibrous tumors of the jaw and kidney in HPT-JT.[3] It has not been established whether familial isolated hyperparathyroidism is a variant or an early stage of MEN-1 syndrome.

The disorder usually appears between 20 and 25 years, as in our index case, and approximately 30 years earlier than in the case of sporadic PHPT. The affected patients show multi-gland involvement, with a lower cure rate and an increased risk of recurrent PHPT and carcinomas compared with sporadic PHPT.[1,4] In addition, they develop severe hypercalcemia more often than patients with MEN-1.[3]

The disorder exhibits an autosomal dominant hereditary trait, with the existence of no specific gene. However, germinal mutations in *MEN-1*, *HRPT2* and *CASR* have been described in a significant number of families, so mutations of the same gene may be responsible for different syndromes.[1,5]

The clinical manifestations are severe, and the histological findings are usually consistent with adenomas or carcinomas, as in our case. Hyperplasias are less common. However, no patients showed cystic changes in the histopathological study, typical of HPT-JT.[1]

Recently, a germinal mutation in *GCM-2* has been described in families with familial isolated hyperparathyroidism, characterized by higher PTH levels, a greater risk of multi-gland disease and carcinoma, and with a lower biochemical cure rate.[6,7]

On the other hand, mutation of the *HRTP2 (CDC73)* gene is identified in 15–20% of all sporadic parathyroid gland carcinomas. As a result, some authors[4,5] consider it to be a tumor suppressor gene. Patients with newly diagnosed parathyroid carcinoma should undergo a careful review of their family history and should be offered a genetic study for *HRTP2* gene mutation.[3]

Asymptomatic carriers require optimal prospective monitoring, including neck ultrasound and periodic serum calcium and PTH measurements, in order to ensure early detection of the disease.[8]

While the indication of surgery for the management of sporadic PHPT is well established, the treatment of choice

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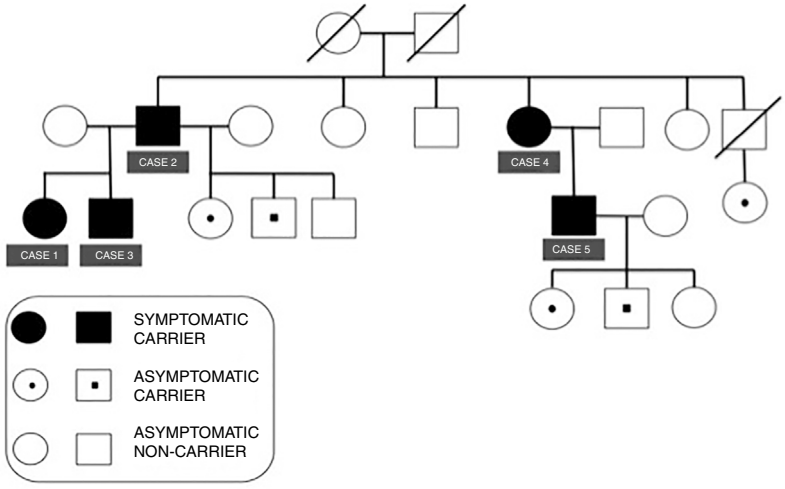

CASE	AGE AT DIAGNOSIS	GENDER	CALCIUM (8.5-10.5 mg/dl)	PTH (10-65 pg/ml)	PARATHYROID HISTOLOGY
1	20	F	12.5	209	Hyperplasia
2	50	M	1	131	Carcinoma
3	29	M	10.3	95	Hyperplasia
4	56	F	9.8	52	Pending surgery
5	37	M	11.9	147	Adenoma

Figure 1 Family tree of the family with familial isolated hyperparathyroidism, with mutation of the *HRPT2* gene. Table summarizing the principal characteristics of the cases.

in patients with familial isolated hyperparathyroidism associated with *HRPT2* remains controversial. Several authors[8,9] argue that in view of the high rate of recurrence or persistence of the disease, the morbidity associated with repeat surgery, and the risk of developing parathyroid carcinoma,[8,10] a subtotal parathyroidectomy should become the initial strategy in patients with mutation of the *HRPT2* gene. Other authors suggest that total parathyroidectomy is the best treatment strategy, even in the absence of suspected cancer.[3] We advocate subtotal parathyroidectomy with thymectomy to avoid the development of parathyroid carcinomas.

In cases of PHPT in young adults, particularly when associated with a family history of PHPT and in the absence of other syndromic conditions, it is important to extend genetic studies to other mutations in addition to *MEN-1*, including *HRPT2*. In families with familial isolated hyperparathyroidism and mutation of the *HRPT2* gene, close monitoring of asymptomatic carriers is crucial, and a more aggressive surgical approach is recommended in patients with PHPT because of the increased risk of developing parathyroid carcinoma.

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References

1. Iacobone M, Carnaille B, Palazzo FF, Vriens M. Hereditary hyperparathyroidism – a consensus report of the European Society of Endocrine Surgeons (ESES). Langenbecks Arch Surg. 2015;400:867–86.
2. Barczynski M, Konturek A, Hubalewska-Dydejczyk A, Cichon S, Nowak W. Evaluation of Halle, Miami, Rome, and Vienna intraoperative iPTH assay criteria in guiding minimally invasive parathyroidectomy. Langenbecks Arch Surg. 2009;394:843–9.
3. Pontikides N, Karras S, Kaprara A, Anagnostis P, Mintziori G, Goulis DG, et al. Genetic basis of familial isolated hyperparathyroidism: a case series and a narrative review of the literature. J Bone Miner Metab. 2014;32:351–66.
4. Howell VM, Haven CJ, Kahnoski K, Khoo SK, Petillo D, Chen J, et al. *HRPT2* mutations are associated with malignancy in sporadic parathyroid tumours. J Med Genet. 2003;40:657–63.
5. Ghemigian A, Ghemigian M, Popescu I, Vija L, Petrova E, Dumitru NE, et al. Familial isolated primary hyperparathyroidism due to HRPT2 mutation. Hormones (Athens). 2013;12:454–60.
6. Guan B, Welch JM, Sapp JC, Ling H, Li Y, Johnston JJ, et al. *GCM2*-Activating mutations in Familial Isolated Hyperparathyroidism. Am J Hum Genet. 2016;99:1034–44.
7. El Lakis M, Nockel P, Guan B, Agarwal S, Welch J, Simonds WF, et al. Familial isolated primary hyperparathyroidism associated with germline *GCM2* mutations is more aggressive and has a lesser rate of biochemical cure. Surgery. 2018;163:31–4.
8. Guarnieri V, Scillitani A, Muscarella LA, Battista C, Bonfitto N, Bisceglia M, et al. Diagnosis of parathyroid tumors in familial isolated hyperparathyroidism with *HRPT2* mutation:

implications for cancer surveillance. J Clin Endocrinol Metab. 2006;91:2827–32.
9. Sarquis MS, Silveira LG, Pimenta FJ, Dias EP, Teh BT, Friedman E, et al. Familial hyperparathyroidism: surgical outcome after 30 years of follow-up in three families with germline *HRPT2* mutations. Surgery. 2008;143:630–40.
10. Silveira LG, Dias EP, Marinho BC, Gomez RS, de Marco L, Sarquis MS. *HRPT2*-related familial isolated hyperparathyroidism: could molecular studies direct the surgical approach? Arq Bras Endocrinol Metab. 2008;52:1211–20.

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The first reported case of *struma cordis* in Spain☆

El primer caso descrito de *struma cordis* en España

Introduction

Struma cordis, or cardiac ectopic thyroid tissue, is a rare condition that affects 1 in every 100,000–300,000 people, and is mostly diagnosed in middle-aged women.[1]

The thyroid primordium starts between days 24 and 32 of pregnancy from a thickening of the endodermal epithelium located at the base of the embryonic midline. In turn, the base of the tongue forms and is commonly referred to as the foramen or blind orifice. The appearance of ectopic thyroid tissue is the result of aberrant embryogenesis during migration of the thyroid primordium in the fourth week of pregnancy. Such migration normally takes place from the foramen to the typical thyroid gland location anterior to the second-fourth tracheal cartilage.[1,2]

According to necropsy studies, the prevalence of ectopic thyroid tissue ranges between 7 and 10%, and the diagnosis is usually established in the first three decades of life. The most common site of appearance is the base of the tongue (in up to 90% of cases), though thyroid remnants may be found over the entire trajectory of the thyroglossal duct, and even in the mediastinum.[2] The first case of intrapericardial ectopic thyroid tissue was reported following necropsy in 1941.[3] In most reported cases, the thyroid tissue is located in the interventricular septum or right ventricle, with obstruction of the right ventricular outflow tract.[2,4]

Case report

We present the first case of *struma cordis* described in Spain. The patient was a 28-year-old woman with no relevant disease history or toxic habits, referred to Cardiology for the evaluation of a heart murmur of recent onset.

She had no dyspnea, chest pain or other evidence of heart failure. The physical examination revealed little more than a mild tricuspid systolic murmur at auscultation.

The blood tests and electrocardiographic findings were within normal limits. Transthoracic (TTE) and transesophageal echocardiography (TEE) revealed a 3.5 cm^3 broad-pedicled and scantly mobile tumor lesion in the intraventricular septum of the right ventricle, close to the tricuspid valve (Fig. 1).

A midline sternotomy was performed, with a right atriotomy and removal of the well delimited mass supported by the interventricular septum. The pathology study revealed the presence of ectopic thyroid tissue with focal fibrosis and dystrophic calcifications. There were no signs of malignancy.

Following the histological findings, a neck ultrasound study was carried out to verify the presence of eutopic thyroid tissue, and thyroid function testing after surgery showed TSH 1.3 mU/l (reference range: 0.25–5). Thyroid scintigraphy revealed a single focus of radiopharmaceutical uptake in the anterocervical region.

Discussion

Although the molecular mechanisms underlying thyroid dysgenesis are not fully understood, mutations of genes *TITF-1* (*Nkx2-1*), *Foxe1* (*TITF-2*) and *PAX-8* have a crucial impact upon thyroid morphogenesis and differentiation, and may cause alterations in thyroid migration, as well as conditioning the appearance of ectopic thyroid tissue remnants. The literature on this subject is scarce, though cases with familial aggregation have been reported.[1]

Most cases of thyroid ectopia are located on the midline of the neck along the trajectory of the thyroglossal duct from the base of the tongue to the diaphragm, and coexist with normal thyroid tissue. The clinical manifestations of thyroid ectopia range from the absence of symptoms to altered thyroid gland function. The most common manifestation of thyroid dysfunction is the appearance of hormonal hypofunction, which in turn is related to the amount of ectopic thyroid tissue. However, symptoms of hyperthyroidism have been reported, even with histological features similar to those of Graves' disease. Depending

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