REVIEW

Primary hyperparathyroidism in multiple endocrine neoplasia type 1: when to perform surgery?

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Primary hyperparathyroidism is a common endocrinological disorder. In rare circumstances, it is associated with familial syndromes, such as multiple endocrine neoplasia type 1. This syndrome is caused by a germline mutation in the multiple endocrine neoplasia type 1 gene encoding the tumor-suppressor protein menin. Usually, primary hyperparathyroidism is the initial clinical expression in carriers of multiple endocrine neoplasia type 1 mutations, occurring in more than 90% of patients and appearing at a young age (20–25 years). Multiple endocrine neoplasia type 1/primary hyperparathyroidism is generally accompanied by multiglandular disease, clinically manifesting with hypercalcemia, although it can remain asymptomatic for a long time and consequently not always be recognized early. Surgery is the recommended treatment. The goal of this short review is to discuss the timing of surgery in patients when primary hyperparathyroidism is associated with multiple endocrine neoplasia type 1.

KEYWORDS: Primary hyperparathyroidism; Multiple endocrine neoplasia 1; PHPT-MEN1; Subtotal parathyroidectomy; Total parathyroidectomy.

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is a condition caused by hyperfunction of the parathyroid tissue, usually involving only one gland. However, it is often multiglandular when expressed within complex hereditary syndromes, such as multiple endocrine neoplasia type 1 (MEN1), MEN2A, familial isolated hyperparathyroidism, autosomal dominant mild hyperparathyroidism, neonatal severe hyperparathyroidism, familial hypocalciuric hypercalcemia, and the hyperparathyroidism–jaw tumor syndrome (1,2).

Surgery is the principal treatment for these forms of familial PHPT, apart from in cases associated with familial hypocalciuric hypercalcemia. In this short review, we discuss the timing of surgery in patients with PHPT associated with MEN1.

MEN1 SYNDROME

MEN1 syndrome (MIM#131100) is a rare hereditary cancer syndrome encompassing a variety of more than 20 endocrine and nonendocrine tumors (3). MEN1 is relatively rare (approximately 1 in 30,000) and the definition of MEN1 that is widely used is ''a case with tumor in two of the three principal organs: anterior pituitary, parathyroid, and enteropancreatic endocrine tissue'' (4,5).

Familial MEN1 is defined as one MEN1 case plus one first-degree relative with one of the three principal tumors or involvement of only one organ and a MEN1 disease-causing germline mutation (6).

The *MEN1* gene was identified in 1997 and is the only gene known to be associated with this syndrome (7,8). Genetic testing with direct sequencing of the *MEN1* gene is widely available and provides the best method of diagnosis; it can detect *MEN1* gene mutations in about 90% of patients with MEN1 within 4–6 weeks. Germline *MEN1* mutation is identifiable in 90% of typical MEN1 families and in only 6–10% of isolated cases (9). Some patients without an identified mutation may have large deletions that are not recognized by polymerase chain reaction or have mutations in the tested open reading frame and intron–exon junctions (10,11). Recently it became possible to search for large deletions or duplications in the *MEN1* gene using the multiplex ligation-dependent probe amplification assay (12).

Genetic testing makes possible: (a) the identification of asymptomatic adults with a family history of MEN1; (b) the prenatal diagnosis of MEN1; and (c) the elimination of non-carriers by clinical screening (13).

MEN1-PHPT

PHPT in MEN1 is the most common form of endocrinopathy and it represents 2–4% of all forms of PHPT. It is the

No potential conflict of interest was reported.

earliest endocrine expression in most patients, clinically relevant neoplasia is uncommon before puberty, occurring in 90% of MEN1 individuals between 20 and 25 years of age, although mild-to-moderate hyperparathyroidism often emerges during adolescence with mild hypercalcemia. All individuals are affected by 50 years of age (14). Its progression is usually gradual but significant hypercalcemia is occasionally evident in early adolescence.

The signs and symptoms of hypercalcemia include kidney stones, low bone mass, constipation, nausea, vomiting, polyuria, dehydration, hypercalciuria, hypertension, shortened QT interval, lethargy, depression, confusion, and anorexia (14).

The medical therapies of MEN1-related PHPT include drugs such as bisphosphonates and calcimimetics. Currently, these drugs have a limited role, being used primarily in the presence of recurrent PHPT or when there are contraindications to surgery (15–17).

The treatment of choice in MEN1-related PHPT is surgery but in this regard some considerations deserve attention.

Age

The age of onset of familial hyperparathyroidism is clearly anticipated at two–three decades compared with the non-syndromic form. The occurrence of hyperparathyroidism at a young age carries a high suspicion of MEN1 syndrome, supported by family history and an association with other endocrinopathies typical of MEN1 syndrome (13). Preclinical diagnosis of *MEN1* gene mutations should be offered to all patients with suspected genetic disease (18).

With presymptomatic detection of genetic predisposition to this syndrome, patients can be followed with periodic clinical tumor surveillance for expression of the disease as well as for recurrence after treatment or progression of the disease; knowledge of carrier status enables early intervention (3).

Genotype–phenotype correlation regarding the severity of PHPT in MEN1 cannot be identified (18,19) but knowledge decreases the uncertainty and anxiety in the patient and allows focused surveillance by the physician.

Parathyroid tissue

Generally the PHPT is caused by a multiglandular disease and the parathyroid glands can become hyperplastic or develop adenomas. The growth of the glands is asynchronous and asymmetric (18), as each gland is considered to be a monoclonal lesion in which the germline mutation in the *MEN1* gene confers on the parathyroid tissue a high susceptibility for the development of a tumor after the second somatic mutation (2,20).

Morphologically, parathyroid glands in MEN1 may appear macroscopically normal, also because they can differ in terms of volume, weight, and size (18).

Parathyroid adenomas in MEN1 can be ectopic, often located in the thymus, rarely within the thyroid gland, in the anterior mediastinum, in the pericardium, or surrounding the trachea, the esophagus, and the carotid artery (21–23).

Supernumerary glands are frequently found in up to 20% of MEN1 patients, although some authors do not report supernumerary glands (18). A possible explanation for this discrepancy may be the misinterpretation of the size, shape or position of the parathyroid glands in MEN1 (18) because of different surgical strategies used; some of which are more capable of identifying supernumerary glands that would otherwise go unnoticed (24).

Biochemistry and bone mineral density

In young MEN1 patients, PHPT is often asymptomatic; mild ionized hypercalcemia with parathyroid hormone (PTH) within the normal range is typical (25).

However, it should be remembered that PHPT is defined as an excess of PTH with consequent increase in bone turnover, leading to a reversible loss of cortical and trabecular bone caused by an expansion of the remodeling space and a loss of cortical for increased endocortical resorption (26). MEN1 hyperparathyroid patients show more precocious and severe bone loss compared with patients with sporadic PHPT (27–31).

Surgical approaches

The optimal surgical approach in PHPT in MEN1 is still under discussion. The choice being between: subtotal parathyroidectomy with removal of at least three to three and a half glands; and total parathyroidectomy with removal of all parathyroid glands and autologous parathyroid tissue graft.

Subtotal parathyroidectomy requires the identification of all parathyroid glands and the leaving of a remnant the size of a normal parathyroid, approximately 20–30 mg. The dissection must be meticulous to preserve the delicate single end-artery vascular supply to the parathyroid remnant. The parathyroid tissue left *in situ* should be prepared before resection of the remaining glands, to avoid bleeding and ischemia. Moreover, this residue must be marked with a non-absorbable suture or a surgical clip for future identification. It may be useful to suture the residual remnant gland away from the recurrent laryngeal nerve to facilitate reoperative surgery in case of persistent or recurrent disease (18,32,33).

Total parathyroidectomy provides identification and resection of all four glands followed by a parathyroid heterotopic auto-implant in the non-dominant forearm (20–25 pieces, 1 mm each, of fresh parathyroid tissue implanted in one to five pockets created in the brachioradialis muscle). This surgical approach must be accompanied by intraoperative histologic examination, to qualify and confirm the presence of parathyroid tissue in the removed tissues, and by rapid intraoperative PTH evaluation (18,32,33).

Reoperative debulking surgery of the forearm graft for recurrent disease can be performed under local anesthesia.

Prophylactic transcervical thymectomy should be performed in all patients to remove possible intrathymic supernumerary parathyroid glands and prevent the development of thymic carcinoid.

Both procedures should include a meticulous search for ectopic parathyroid tissue, which is commonly encountered within the thymus, mediastinum, carotid sheath, and in the tracheo-esophageal groove (21–23).

Extensive surgery is burdened by an increased risk of permanent hypoparathyroidism (hypocalcemia) and recurrent laryngeal nerve injury. Acute hypoparathyroidism may cause mild to severe neuromuscular symptoms ranging from neuromuscular irritability to seizures. Less extensive surgery yields a higher risk of recurrent disease requiring re-intervention, which increases the risk of more complications. In this latter intervention, multiple operations are

often required with a consequent increase in surgical morbidity (18,32,33).

It should be noted that in the hands of an expert surgeon the rate of persistent disease in MEN1-associated PHPT is less than 20%, but this may rise to 40–60% for surgeons with less experience. For example, some MEN1 patients may have only a single macroscopically abnormal gland and might undergo inadequate surgery (34).

DISCUSSION

The optimal treatment of PHPT in MEN1 is parathyroidectomy, as it reduces the risk of kidney stones, fractures (improved bone mineral density), and potential cardiovascular morbidity, improving quality of life and reducing gastrin production in MEN1 patients who also have a gastrinoma (35).

Some authors think that parathyroid surgery in patients with MEN1 should be thought of as a debulking or palliative procedure because long-term recurrence is inevitable. Surgery being indicated to treat and prevent the complications of hyperparathyroidism (24).

There are also disputes about surgical timing in patient with MEN1. The surgical indication for PHPT is obvious in patients with symptoms or with severe hypercalcemia; and in these circumstances there appears to be a good risk/benefit balance. However, if MEN1 syndrome has not been diagnosed preoperatively and if an experienced surgeon is not available, then surgical treatment might not be appropriate (18).

In young patients with asymptomatic, mild hypercalcemia the timing of surgery is controversial, given that recurrence rates increase in relation to the follow-up time.

According to our experience, biochemical screening for hyperparathyroidism is recommended, as well as for the other MEN1-related tumors, and it should be performed regularly in carriers of an *MEN1* mutation. This is because clinical manifestation can be mild for long periods of time, but a lack of regular screening may result in the delay of diagnosis and in the development of complications (36).

Total serum calcium concentration corrected for albumin level or ionized calcium fraction was proposed as a single sufficient screening test for hyperparathyroidism in MEN1 (37). However, increased PTH has been observed in MEN1 patients with mild PHPT even in the absence of hypercalcemia, making it necessary to include serum PTH concentration measurement in the screening program (38).

Imaging is not necessary for the diagnosis of parathyroid disease in MEN1 for known multiglandular involvement, but the presence of an experienced MEN1 surgeon is certainly recommended (14).

Assessment of bone mass loss by densitometry is essential in PHPT, mostly in MEN1 patients who have PHPT during the bone mass accretion period (26–31). Lourenço et al. (39) clearly indicated that bone demineralization in MEN1 PHPT patients was early in onset, progressive, frequent, extensive, and severe. Surgery is the most effective way to preserve bone mass in patients with MEN1 PHPT (20).

Therefore, surgery is recommended in young asymptomatic patients in whom the serum calcium values are more than 1 mg/dl over the upper-normal limit and whose bone mineral density values are lower than –2.5 T-score.

Early parathyroidectomy predisposes the patient to an earlier recurrence of hyperparathyroidism and the possibility of progressively challenging reoperations. Late surgical interventions are easier because of the glands' more visible enlargement, but hypercalcemic complications increase.

The diagnosis of MEN1-associated PHPT should be confirmed by genetic testing. Carriers of *MEN1* mutations require regular screening, regardless of the presence of hyperparathyroidism from the second decade of life, it being difficult to establish a genotype–phenotype relation. When gene carriers are studied prospectively, biochemical evidence of neoplasia can be detected as early as 5–10 years before clinically evident disease, allowing for early surgical intervention and therefore dramatically reducing both the morbidity and the mortality related to the syndrome. Surgery remains the main method of PHPT management in MEN1, despite the high recurrence rate with the need for repeat procedures. Some controversies surround the optimal surgical technique for MEN1 PHPT. The optimal timing for surgery remains controversial and must be assessed case by case without forgetting that the complications of PHPT in MEN1 are early in onset and more severe than in sporadic PHPT. Medical therapy with the goal of bone preservation is an option for patients without symptoms, and calcimimetics effectively normalize calcium levels only with specific indications.

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AUTHOR CONTRIBUTIONS

All the authors were responsible for the manuscript writing.

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