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Editorial

Surgical Management of Familial Hyperparathyroidism

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In the February 2007 issue of the journal, the members of the Section of Endocrine Surgery at the University of Wisconsin under the leadership of Dr. Herb Chen report their experience with radioguided parathyroidectomy in 19 patients with familial hyperparathyroidism (HPT).[1] The cause of HPT was multiple endocrine neoplasia type 1 (MEN1) in 11 patients, multiple endocrine neoplasia type 2 (MEN2) in 1, and presumed nonsyndromic or familial isolated HPT (FIHPT) in 7. The gamma probe accurately localized all hyperplastic parathyroid glands and when combined with the intraoperative parathyroid hormone (IOPTH) assay resulted in the correction of hypercalcemia (at least in the short term) in all 19 patients. Such excellent results require accurate intraoperative identification of the parathyroid glands, including those that may exist in ectopic locations, as well as a thorough understanding of the natural history of the familial syndromes associated with HPT to allow for the proper management of the parathyroids once they are identified. Finding the parathyroid glands is of value only if one knows how many to remove, when to cryopreserve, and when and where to autograft; the gamma probe is just one piece of the puzzle necessary to generate the results as seen from the University of Wisconsin.

Familial HPT is caused by several known inherited disorders, but it may also occur in nonsyndromic form with autosomal dominant inheritance or familial tendency. Syndromic disorders in which HPT is a central feature include MEN1 and MEN2A, hyperparathyroidism jaw tumor syndrome (HPT-JT), and familial hypocalciuric hypercalcemia (FHH). The genetic basis of nonsyndromic HPT or FIHPT is unknown, but recent evidence suggests that a causative gene for FIHPT may reside on chromosome 2.[2]

Patients with MEN1 typically develop HPT due to hyperplasia of multiple parathyroid glands in early adulthood and essentially all are affected by age 50, though HPT may go undiagnosed for years.[3] Most patients with MEN1 have one or more affected relatives with autosomal dominant transmission of disease. In 75% to 90% of affected families, a causative germline mutation has been identified in the putative tumor suppressor gene, *MEN1*, located on chromosome 11q13. More than 400 different germline mutations in *MEN1* have been reported and are scattered throughout the coding region (exons 2 through 10) as well as in splice sites within noncoding introns. Most mutations are unique to individual families without marked clustering or correspondence to protein functional domains that would suggest genotype-phenotype correlations. Several functional roles for menin (protein product of the *MEN1* gene) have been proposed, including regulation of DNA replication and repair, transcriptional activation, and chromatin modification. Patients with MEN1 also commonly develop functioning and nonfunctioning tumors of the pancreatic islet cells and duodenum, and the anterior pituitary gland. Less commonly, they may develop bronchial and thymic carcinoid tumors, adrenal tumors, thyroid neoplasms, and/or meningiomas.[4]

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MEN2 is an autosomal dominant inherited predisposition to the development of medullary carcinoma of the thyroid (MTC) with three main subtypes; MEN2A, MEN2B, and familial MTC. In contrast to MEN1, where there is near-complete penetrance of HPT, hypercalcemia develops in only 20% to 30% of patients with MEN2A and does not occur in MEN2B or familial MTC, which is defined as inherited medullary thyroid cancer without other endocrine tumor susceptibility. Pheochromocytoma is present in approximately half of patients with MEN2A or MEN2B. Germline point mutations of the *RET* (*re*arranged during *t*ransfection) proto-oncogene are responsible for MEN2. The *RET* gene is a member of the cadherin superfamily located on chromosome 10q11.2.[5] The gene contains 21 exons and encodes a single-pass membrane receptor tyrosine kinase. Unlike MEN1, strong genotype-phenotype correlations exist for specific *RET* codon mutations, the clinical subtype of MEN2, and the age at onset and aggressiveness of MTC.[6] HPT in MEN2A is most often associated with the codon 634 mutation (specifically a cysteine-to-arginine amino acid substitution) and less commonly with mutations in codons 609, 611, 618, 620, 790, and 791.

HPT-JT syndrome is an extremely rare condition in which HPT occurs in association with ossifying fibromas of the maxilla or mandible (one-third of patients), and parathyroid carcinoma (10% to 15% of patients). Inactivating germline mutations of the *HRPT2* (hereditary hyperparathyroidism type 2) gene on chromosome 1q25-31 are identified in most, but not all, cases of HPT-JT.[7] HPT has a penetrance of approximately 80% and typically manifests during young adulthood. In contrast to other forms of inherited HPT, hypercalcemia is usually due to a single parathyroid adenoma (or carcinoma) that frequently has a cystic component. *HRPT2* is also inherited in an autosomal dominant pattern, and its protein product is thought to function as a tumor suppressor gene. *HRPT2* consists of 17 coding exons and encodes a 531 amino acid protein, parafibromin, which is the human homologue of the yeast protein, Cdc73p. Cdc73p is a component of the RNA polymerase II associated Paf1 complex, which functions throughout several stages of the yeast transcription cycle.

FHH is usually associated with inactivating germline mutations in the calcium-sensing receptor (*CASR*) gene on chromosome 3q13-21, resulting in reduced function of the extracellular calcium-sensing receptor. The calcium sensing receptor is part of the 7-membrane-spanning G protein-coupled receptor superfamily and functions in maintaining extracellular calcium ion homeostasis. Normally the calcium-sensing receptor serves to respond to increased extracellular calcium ion concentration by decreasing *PTH* gene expression, PTH secretion, and parathyroid cellular proliferation, and by increasing calcium ion secretion in the kidney. Thus, inactivation of the receptor results in the clinical picture of (asymptomatic) mild to moderate hypercalcemia with inappropriately normal parathyroid hormone levels, relative hypocalciuria, and a calcium/creatinine clearance ratio of less than .01. In these individuals, parathyroidectomy does not correct the hypercalcemia. There may also be a subtype of FHH associated with familial chronic pancreatitis as a result of coinheritance of the pancreatic secretory trypsin inhibitor gene *SPINK1*.[8]

Some cases of apparent FIHPT have been found to harbor germline mutations in *MEN1*, *CASR*, and *HRPT2*, suggesting incomplete expression of syndromic forms of inherited HPT. Most FIHPT families do not have identifiable mutations, although recent studies have linked a FIHPT locus to chromosome 2p14-p13.3 *(HRPT3)*.[2] In patients with FIHPT, genetic screening for MEN1 and FHH is most likely to identify mutations in those with young age at onset and multigland parathyroid involvement, whereas *HRPT2* mutations should be considered in those families with parathyroid carcinoma, cystic parathyroid tumors, or jaw tumors. Interestingly, somatic mutations (in the tumor DNA) of the *MEN1* gene have been found in sporadic parathyroid adenomas, and somatic mutations of *HRPT2* have been found in parathyroid carcinoma, an observation that provides additional support for a role of these two genes in the aberrant growth of parathyroid cells.

The operative management of patients with familial HPT is complicated. For the symptomatic patient, the decision to proceed with surgery is easy. However, indications for parathyroidectomy in asymptomatic MEN (MEN1 and MEN2) patients are less well defined because MEN-associated HPT occurs at an earlier age, is characterized by multigland hyperplasia, and is associated with a high rate of recurrent HPT after initial parathyroidectomy. Because surgery is the most effective strategy for preserving bone density in patients with HPT, bone density evaluation should play an important role in planning the timing of parathyroid surgery in MEN patients with asymptomatic HPT. In addition, the neuropsychiatric manifestations of HPT may affect the patient with MEN who is otherwise thought to be asymptomatic. HPT is believed to affect sleep, cognition, mood, and

overall quality of life. For patients with MEN1, we advocate removal of three of the four parathyroid glands and a transcervical thymectomy at the first operation.[3] The parathyroid gland of smallest size is typically left in situ. If the gland to be left in situ is not larger than two times normal size, then it is left undisturbed; partial resection is considered for larger glands. A transcervical thymectomy is performed because of the potential for an ectopic parathyroid gland, because it or may not represent a supernumerary gland, and which may reduce the risk of development of a thymic carcinoid. If the IOPTH remains measurable, we do not perform a parathyroid autograft at the initial operation. If recurrent HPT develops after an initial subtotal parathyroidectomy, completion total parathyroidectomy can be combined with forearm autografting. In all patients with inherited HPT, parathyroid autografts, when performed, should be placed in the forearm to facilitate the diagnosis of parathyroid autograft hyperfunction and to allow for easy autograft debulking. Our recent experience with MEN1-related HPT documented a long delay in autograft function in some patients and autograft hyperfunction in others.[3]

The management of the parathyroid glands in patients with MEN2A presents other unique surgical challenges. For example, in contrast to MEN1 (where the indication for neck exploration is limited to HPT), patients with MEN2A undergo prophylactic or therapeutic thyroidectomy, often at an early age, when there is no biochemical evidence of HPT. In such patients, only grossly enlarged parathyroids should be removed (and cryopreserved), and an autograft should not performed in the neck if the *RET* mutation is associated with MEN2A.[9] Patients with MEN2A who develop HPT have often undergone prior thyroidectomy, usually with a central compartment (level VI) dissection, and may or may not have all glands remaining in situ. In such patients, preoperative localization and the use of the gamma probe and IOPTH become even more important to a successful outcome. Although HPT is diagnosed in only 20% to 30% of MEN2A patients (predominantly those with the codon 634 mutation) and may involve just one or two glands, our experience suggests that MEN2A-associated HPT is often a multigland disease and is as tricky to manage as in MEN1 patients.

In patients with clear evidence of FIHPT by pedigree analysis, genetic screening should be performed in at least one affected individual for MEN1, CASR, or HRPT2 depending on the clinical features present. The diagnosis of FHH due to a mutation in CASR would support a nonoperative approach to HPT, especially in the presence of an asymptomatic patient with well-preserved bone mass. The presence of a mutation in the *HRPT2* gene should alert the surgeon to the potential for parathyroid carcinoma and the high likelihood of single gland disease. Importantly, the surgical management of parathyroid carcinoma, when recognized intraoperatively as a large gray-white invasive mass, requires en-bloc resection of the thyroid lobe and attached soft tissues (everything but recurrent nerve, trachea, and esophagus) on the side of the lesion. There is usually only one chance to cure parathyroid carcinoma, and that lies at the initial operation. Parathyroid carcinoma, if incompletely resected or fractured, has the propensity to disseminate into surrounding soft tissues, muscle, and esophagus.

The management of patients with familial HPT is complicated both in and out of the operating room. The gamma probe may represent a valuable tool, but only if operated by a skilled and experienced endocrine surgeon. The University of Wisconsin experience may be hard for the rest of us to duplicate.

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