

Multiple Endocrine Neoplasia TYPE 2

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Background

Type 2 multiple endocrine neoplasia (MEN 2) is a rare familial cancer syndrome caused by mutations in the *RET* proto-oncogene. Sipple first described an association between thyroid cancer and pheochromocytoma (benign tumor of the adrenal medulla) in 1961. The thyroid cancer found with pheochromocytoma was discovered in 1965 to be a medullary carcinoma characterized by stromal amyloid. In 1968, this familial constellation of pathology in conjunction with parathyroid hyperplasia was recognized as MEN 2.

Although patients with mucosal neuromas were identified at this time, the distinction between MEN 2A and MEN 2B was not made until 1975. The differences between these variations of the disease are as follows:

- Phenotype - MEN 2A patients do not have the phenotypic abnormalities of mucosal neuromas and marfanoid habitus found in MEN 2B patients
- Medullary thyroid carcinoma - MEN 2A patients have a less virulent form of medullary thyroid carcinoma than do MEN 2B patients
- Parathyroid hyperplasia - MEN 2A patients may have parathyroid hyperplasia, which is exceedingly rare in MEN 2B patients

A third subtype of MEN 2 is familial medullary thyroid carcinoma only (FMTC only).

Epidemiology

The overall frequency of MEN 2 in the United States is 1 case per 30,000-50,000 persons in the United States. In decreasing order of frequency, MEN occurs as follows: MEN 2A, FMTC only, and MEN 2B.

In MEN 2A patients, 50% of those with *RET* gene mutations develop the disease by age 50 years, and 70% develop the disease by age 70 years. Medullary thyroid carcinoma has been detected shortly after birth in MEN 2B.

Patient education

Adhering to a surveillance program lessens disease complications. Order genetic counseling for the patient so that gene testing and reproductive options can be discussed. For patient education information, see Thyroid Problems. (See Treatment.)

Pathophysiology

As previously stated, MEN 2 is a rare familial cancer syndrome caused by mutations in the *RET* proto-oncogene. Inherited as an autosomal dominant disorder, MEN 2 has 3 distinct subtypes,

including MEN 2A, MEN 2B, and FMTC only. The subtypes are defined by the combination of tissues affected. Developmental abnormalities may also be present.

By age 70 years, the penetrance rate is 70%. Genetic testing and clinical surveillance beginning in childhood provide the opportunity to treat the devastating and sometimes fatal complications of this disorder.^[1]

The *RET* proto-oncogene is 80 kilobases (kb) long and encodes a putative tyrosine kinase receptor. Its endogenous ligand may be glial cell line-derived neurotrophic factor (GDNF), which appears to play a critical role in the normal function of pathways involved in enteric nervous system neurogenesis and renal organogenesis.

Data suggest that an overrepresentation of mutant *RET* as an undefined second hit event may trigger tumorigenesis. However, alterations in other genes may contribute to this overrepresentation of *RET* or may influence MEN 2-related tumor development through completely different mechanisms and pathways.

Glandular hyperplasia begins with an increase of C cells located in the thyroid gland follicles and can progress to malignancy.

Medullary thyroid carcinoma

Virtually all patients with MEN 2A develop medullary thyroid carcinoma. This is often the first expressed abnormality and usually occurs in the second or third decade of life. The medullary thyroid carcinoma in patients with MEN 2A is typically bilateral and multicentric, in contrast to sporadic medullary thyroid carcinoma, which is unilateral.

Pheochromocytoma

Pheochromocytomas are present in approximately half of MEN 2A patients. They are bilateral in 60-80% of patients, compared with 10% of patients with sporadic pheochromocytomas. Pheochromocytomas tend to be diagnosed at the same time as medullary thyroid carcinoma or several years later (with both occurring primarily in the second or third decade). The pheochromocytomas of MEN 2A patients are nearly all benign. Even so, these lesions can cause a life-threatening hypertensive episode or arrhythmia.

Parathyroid hyperplasia

Parathyroid hyperplasias are present in nearly half of patients with MEN 2A but are less common than pheochromocytomas. In many patients, such hyperplasias can be clinically silent. However, as in other cases of hyperparathyroidism, symptoms can often be elucidated following comprehensive questioning.

Mutations in *RET*, a transmembrane proto-oncogene, have been localized to 10q11.2 and are responsible for MEN 2. Although its function is still unknown, the protein produced by *RET* is critical during embryonic development of the enteric nervous system and kidneys. *RET* consists of 3 domains, including a cysteine-rich extracellular receptor domain, a hydrophobic transmembrane domain, and an intracellular tyrosine kinase catalytic domain.

Point mutations associated with MEN 2A and the FMTC-only subtype were identified in exons 10 and 11. Evidence of genotype/phenotype correlation exists. Almost all individuals with MEN 2B have an identical mutation in codon 918 of exon 16. Inheritance is autosomal dominant, with variable penetrance and expressivity.

Substantiation of the genotype-phenotype correlation of inherited medullary thyroid carcinoma may lead to the development of an individual approach to risk management in childhood genotype carriers, and research into potential modifying factors should take place. Early total thyroidectomy remains effective in preventing the development of medullary thyroid carcinoma in the long-term.^[2]

Prognosis

Early treatment of medullary thyroid carcinoma can prevent death, and careful monitoring for pheochromocytomas can decrease the chance of hypertensive episodes.

MEN 2A, MEN 2B, and the FMTC-only subtype elicit overlapping and distinct abnormalities. The characteristic tumor of MEN 2 medullary thyroid carcinoma is present in all subtypes. Pheochromocytomas appear in MEN 2A and MEN 2B patients. Primary hyperparathyroidism frequently develops in patients with MEN 2A but rarely in those with MEN 2B. Gastrointestinal, skeletal, and dermatologic abnormalities occur only in patients with MEN 2B.

Medullary thyroid carcinoma

The prognosis of medullary thyroid carcinoma is associated with the disease stage at the time of diagnosis. Because the penetrance of medullary thyroid carcinoma is nearly 100%, perform prophylactic thyroidectomy in infancy for patients with high-risk *RET* mutations or by age 5 years in children with an identifiable *RET* mutation.^[3, 4] For patients who are at risk but who have not had genetic screening, perform annual biochemical screening.

The 5- and 10-year survival rates in patients with medullary thyroid carcinoma and MEN 2A are approximately 90% and 75%, respectively.

Pheochromocytoma

These benign tumors of the adrenal medulla occur in 50% of patients with MEN 2 by the time they are in their late 30s; however, prevalence varies in different families. Pheochromocytomas develop in more than 50% of patients with MEN 2B and can appear during early childhood. The earliest possible detection of these tumors can prevent a hypertensive crisis.

Adrenalectomy should be considered when patients have biochemical confirmation and an adrenal mass or enlargement on imaging. A bilateral adrenalectomy is reserved for bilateral adrenal masses. Subtotal adrenalectomy remains controversial.^[5, 6]

Hyperparathyroidism

Extremely uncommon in MEN 2B patients, parathyroid hyperplasia affects 20-30% of MEN 2A patients. Patients may present with hypercalcemia and other vague symptoms.

History

The most important questions to ask relate to a family history of multiple endocrine neoplasms.

Patients may present with symptoms related to medullary thyroid carcinoma, hyperparathyroidism, or pheochromocytoma. However, clinical presentation is associated with the patient's age. A young patient with an identified *RET* proto-oncogene mutation will probably be asymptomatic. These patients generally have thyroid C-cell hyperplasia without progression to medullary carcinoma.

Virtually all index patients have medullary thyroid carcinoma at the time of diagnosis, although their clinical presentation may be consistent with pheochromocytoma or hyperparathyroidism.

Symptoms in type 2 multiple endocrine neoplasia (MEN 2) can include hypertension, episodic sweating, diarrhea, pruritic skin lesions, or compressive symptoms from a neck mass. Patients with hypercalcemia may present with constipation, polyuria, polydipsia, memory problems, depression, nephrolithiasis, glucose intolerance, gastroesophageal reflux, and fatigue, or they may have no symptoms. They may also lose bone density.

Hypertension

If pheochromocytomas develop, an increase in blood pressure and heart rate may be the only signs. These increases can be chronic or episodic. Some patients have episodes of sweating and headaches.

Diarrhea

If a patient has medullary thyroid carcinoma, he or she may have a history of diarrhea from extensive disease. This may be related to elevated prostaglandin or calcitonin levels.

Chronic constipation

This constant finding in MEN 2B patients results from hyperplasia of the intrinsic autonomic ganglia in the intestinal wall. Infants may fail to thrive.

Pruritic skin lesions

Cutaneous lichen amyloidosis in MEN 2A patients manifests as multiple pruritic, hyperpigmented, lichenoid papules in the scapular area of the back.^[7] These lesions are associated with the deposition of altered cytokeratins rather than of calcitoninlike peptides.

Physical Examination

The physical signs of MEN 2 are extremely variable and often subtle. A neck mass or a dominant thyroid nodule is discovered; anterior neck lymph nodes are nontender, arise insidiously with progressive enlargement, and may signify regional metastasis. Blood pressure and heart rate may be elevated if a pheochromocytoma is present.

The marfanoid habitus of high-arched palate, pectus excavatum, bilateral pes cavus, and scoliosis are observed in MEN 2B patients. Neuromas on the eyelids, conjunctiva, nasal and laryngeal mucosa, tongue, and lips are frequent findings. Patients also have prominent, hypertrophied lips leading to a characteristic facies. Localized pruritus appears over the upper back in MEN 2B patients.

Approach Considerations

Perform genetic screening for *RET* mutations in all index patients. If a mutation is identified, also screen family members who are at risk.

For individuals identified with a mutation or for persons who are at risk, biochemical screening consists of ascertainment of baseline calcitonin levels and of serum calcium and parathyroid hormone (PTH) levels, along with urine collection for catecholamines and metanephrine concentrations. (However, a plasma metanephrine level can be used for screening.)

If a patient's calcitonin level is within reference ranges, a pentagastrin and/or Ca^{++} stimulation test may be used as a guide to assess the necessity of a central compartment or modified neck dissection.

Patients who have been diagnosed with medullary thyroid carcinoma require serial calcitonin (+/- provocative testing) and carcinoembryonic antigen (CEA) testing to assess for persistent or recurrent disease.

Fine-needle aspiration

Avoid the removal of cells from thyroid masses for cytology in patients with type 2 multiple endocrine neoplasia (MEN 2) who have had their diagnosis previously confirmed by either genetic analysis or elevated calcitonin levels. These patients have an established diagnosis, and a biopsy increases the possibility of tumor spread. A fine-needle aspiration biopsy is primarily used in an index patient who presents with a thyroid nodule when the clinician considers the presence of medullary thyroid carcinoma to be unlikely.

Screening for Cancer and Hyperparathyroidism

Screening for medullary thyroid carcinoma is done with the pentagastrin stimulation test, with serum calcitonin measured at baseline and at 2, 5, and 10 minutes. False-positive and false-negative results have been reported.

Urinary catecholamines and metanephrines screen for pheochromocytomas. (If these are elevated, imaging studies of the adrenals are recommended.)

Serum calcium level and PTH levels screen for hyperparathyroidism. An inappropriately elevated PTH level in relation to the serum calcium is consistent with primary hyperparathyroidism. If the 24-hour urine calcium level is low, the presence of familial hypocalciuric hypercalcemic syndrome should be considered.

Imaging Studies

Perform computed tomography (CT) scanning or magnetic resonance imaging (MRI) of the adrenals. A metaiodobenzylguanidine (MIBG) scan is useful for localizing pheochromocytomas.^[8, 9, 10]

If calcitonin levels are elevated at either baseline or with provocative testing, evaluate the chest and abdomen for metastatic disease. Available modalities include CT scanning, MRI, octreotide scanning, and, in some instances, laparoscopy.

Radionuclide scanning may reveal the extent of metastasis. OctreoScan provides a whole-body examination and is used to examine the spread of medullary thyroid carcinoma. The somatostatin analogue octreotide, which is used for the treatment of hormone-related symptoms, is labeled with the isotope indium-111 (¹¹¹In) and injected intravenously. The next day, the patient is examined with a gamma camera, which can detect the accumulation of radioactivity.

Histologic Findings

The tumor in medullary thyroid carcinoma is well demarcated, firm, and grayish white. Polygonal cells are uniform, with finely granular eosinophilic cytoplasm with central nuclei. Amyloid formed from calcitonin molecules is often found. Other findings include the following:

- C-cell hyperplasia - Frequently found; is a precursor in the malignant transformation to medullary thyroid carcinoma.
- Pheochromocytomas - Benign tumors, often bilateral and multifocal, that arise from diffuse hyperplasia of the adrenal medulla
- Parathyroid hyperplasia - In this, overgrowth is the most common finding, although adenomatous changes occur in a small percentage of cases

Staging

TNM classification is used for postoperative staging. (T = the size of the primary lesion, N = the presence or absence of regional lymph node metastatic involvement, and M = the presence or absence of distant metastatic lesions.)

Primary lesions are designated as follows:

- T1 - Tumor 2cm or less in greatest dimension, limited to the thyroid
- T2 - Tumor greater than 2 cm but less than or equal to 4 cm; limited to the thyroid
- T3 - Tumor greater than 4 cm; limited to the thyroid

- T4a - Tumor of any size that extends extrathyroidally and invades subcutaneous soft tissues
- T4b - Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels

Regional lymph node metastatic involvement is designated as follows:

- N0 - No evidence of lymph node metastases
- N1 - Regional lymph node metastasis
- N1a - Metastasis to level VI (central compartment) cervical lymph node(s)
- N1b - Metastasis to unilateral or bilateral cervical nodes or to superior mediastinal lymph node(s)

Occurrence of distant metastatic lesions is designated as follows:

- M0 – No evidence of distant metastases exists
- M1 – Distant metastatic lesions exist

Postoperative staging is as follows:

- Stage I - T1,N0,M0
- Stage II - T2,N0,M0
- Stage III – (T3,N0,M0), (T1,N1a,M0), (T2,N1a,M0), (T3,N1a,M0)
- Stage IVA - (T4a,N0,M0), (T4a,N1a,M0), (T1,N1b,M0), (T2,N1b,M0), (T3,N1b,M0), (T4a,N1b,M0)
- Stage IVB - T4b, any N, M0
- Stage IVC - Any T, any N, and M1

Approach Considerations

Type 2A multiple endocrine neoplasia (MEN 2A) is treated with surgery. Preoperative medical treatment may consist of prostaglandin inhibitors to alleviate diarrhea that may be associated with medullary thyroid cancer.

Evaluation for pheochromocytomas is important because these should be removed before other surgical interventions. This evaluation can be performed before parathyroidectomy or thyroidectomy under a single general anesthetic if the patient is stable.

Pheochromocytoma

Preoperatively, prepare patients with pheochromocytomas by treating them with an alpha-blocker or a tyrosine hydroxylase inhibitor, such as metyrosine, for 1-2 weeks, after which administration of a beta-blocker can be considered. Reports of successful management using a calcium channel blocker rather than an alpha blocker have been noted. Many practitioners routinely treat patients with a beta-blocker, while others selectively treat patients based on blood pressure control and tachycardia.

Hypercalcemia

Patients presenting with severe hypercalcemia should first be hydrated, after which they should be treated with furosemide. If they remain severely hypercalcemic, consider treatment with calcitonin, glucocorticoids, or bisphosphonates (such as pamidronate). While bisphosphonates are most commonly used, cinacalcet, a calcimimetic, can also be effective at reducing serum calcium levels. These patients need urgent parathyroidectomy when calcium levels have been lowered, ideally below 14 mg/dL. Patients who are not surgical candidates may also benefit from cinacalcet.

Thyroid supplementation

Thyroid hormone supplementation is necessary following total thyroidectomy in carriers of *RET* mutations or following a diagnosis of medullary thyroid carcinoma.

Transfer

Transfer patients for surgical intervention if necessary.

Deterrence/prevention

Start annual 24-hour urine collections for catecholamine concentrations to detect pheochromocytoma at the earliest age possible. Begin annual testing of serum calcium and PTH levels at age 10 years.

Outpatient care

Monitor patients for recurrence of medullary thyroid carcinoma with calcitonin, CEA, and +/- provocative calcitonin testing.

Perform annual screening for hyperparathyroidism with serum calcium and PTH levels in MEN 2A patients. Obtain urinary catecholamine levels on an annual basis to assess for pheochromocytoma. Carefully monitor medication dosage and adverse effects.

Consultations

Consultations with the following specialists may be necessary:

- Geneticists
- Endocrinologists
- Oncologists