Multiple endocrine neoplasia 2 (MEN2) is a hereditary syndrome associated with medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism. Unfortunately, a diagnosis of MEN2 often is delayed until after the patient has developed an advanced MEN2-related tumor. Nurses should be familiar with hallmark signs of this syndrome to facilitate an early diagnosis and appropriately refer families for genetic assessment and, ultimately, develop a long-term plan for early detection and intervention for all family members at risk for developing MEN2.

T.M. is a 63-year-old man who presented to his primary care physician with a six-month history of chronic fatigue. Initial testing done by his physician revealed hypercalcemia. T.M. was referred to an endocrinologist, and additional testing demonstrated elevated calcitonin levels, which often are indicative of thyroid dysfunction, either C-cell hyperplasia or medullary thyroid carcinoma. He also had an elevated parathyroid hormone level. Ultrasound evaluation revealed a 1.8 cm x 1.5 cm nodule in the left lobe of the thyroid. A nuclear thyroid scan was ordered and T.M. was referred to the oncology clinic for additional evaluation.

Nursing Assessment and Physical Examination

On assessment, the nurse reviewed T.M.’s past medical and family history. T.M. had a history of depression and hyperlipidemia. A palpable thyroid nodule was noted on physical examination. He complained of recurring episodes of diarrhea and neck pain. Past surgeries included cholecystectomy and a hernia repair. The family history is notable for a paternal uncle who was diagnosed with thyroid cancer at age 45 (see Figure 1). T.M.’s father died at age 39 in a motor vehicle accident. T.M. is married and has a 38-year-old daughter and three sons (ages 40, 36, and 34 years). His daughter has thyroid problems of an unknown etiology. T.M. has 10 grandchildren. He works as a truck driver and is frustrated that he has had to take numerous sick days because of his chronic fatigue.

In T.M.’s case, the combination of hyperparathyroidism, elevated calcitonin levels, and the family history of thyroid cancer was highly suggestive of multiple endocrine neoplasia 2 (MEN2). In light of these findings, T.M. was referred for genetic evaluation and testing that identified a mutation in the RET gene consistent with level 2 (intermediate risk) MEN2. Based on the test results, T.M. underwent a total thyroidectomy with cervical lymph node dissection. Parathyroid exploration revealed a large mass which was excised. Pathology results confirmed bilateral medullary thyroid carcinoma with cervical lymph node metastases and a parathyroid adenoma. T.M.’s daughter and two of his sons (the 34- and 36-year-olds), as well as four grandchildren younger than age 16, also tested positive for the same RET mutation. All family members who tested positive for the RET mutation subsequently underwent prophylactic thyroidectomies. They continue to undergo surveillance for residual thyroid carcinoma, pheochromocytomas (a rare tumor of the adrenal gland), and hyperparathyroidism. (See Figure 2 for descriptions of common problems associated with MEN2.)

Etiology of the Problem

Medullary thyroid cancer (MTC) comprises 3%-10% of all thyroid cancers (Lindor, McMaster, Lindor, & Greene, 2008). Patients with MTC often present with a palpable thyroid nodule. Symptoms that may be associated with MTC include hoarseness, difficulty swallowing, dyspnea, and pain in the throat or neck. Diarrhea, resulting from elevated calcitonin levels, also can be a presenting symptom (Moline & Eng, 2010). About 25%-30% of MTC malignancies are caused by MEN2 (Moline & Eng, 2010). MEN2 is an autosomal-dominant
hereditary syndrome caused by germ-line activating mutations of the \textit{RET} proto-oncogene on chromosome 10q11.2 (Akerström & Stålberg, 2009). MEN2 has a frequency of 1 in 30,000 births (Lindor et al., 2008). Individuals with MEN2 have a greater than 95% chance of developing MTC in their lifetime. The incidence of MTC and other tumors associated with MEN2 encompasses three clinical subtypes: MEN2A, MEN2B, and familial medullary thyroid cancer (FMTC). MEN2A, the most common subtype, is characterized by the presence of MTC in early adulthood, pheochromocytoma, and hyperparathyroidism. MTC generally is the first manifestation of MEN2A, developing most often in those aged 5–25 years (Richards, 2008). About 50% of people with MEN2A will develop a pheochromocytoma, and 20%–30% will develop hyperparathyroidism. Hirschsprung disease is a rare manifestation of MEN2A.

MEN2B is the rarest subtype, accounting for about 5%–10% of MEN2 cases. Patients with MEN2B have early disease onset and aggressive MTC, developing during the first year of life, and associated with early metastasis and mortality. Most patients with MEN2B have spontaneous new \textit{RET} mutations without a positive family history. MEN2B is characterized by MTC in early childhood, and pheochromocytomas occur in 50% of affected people. Hyperparathyroidism is almost never seen in individuals with MEN2B; instead, they often have other physical characteristics, including a tall and slender (marfanoid) body, small benign tumors on the lips and tongue (mucosal neuromas), and gastrointestinal problems secondary to ganglioneuromatosis. Patients with MEN2B often experience delay in diagnosis until mucosal neuromas or palpable thyroid tumors are obvious (Richards, 2008).

FMTC is MTC occurring in multiple members of the same family without the presence of pheochromocytoma or hyperparathyroidism. FMTC accounts for about 35%–40% of MEN2 cases and generally is a milder variant of MEN2. MTC may have later onset with better prognosis (Richards, 2008). The classification of FMTC is clinical and strict: Only families in which four or more cases of MTC exist with documented absence of pheochromocytoma and hyperparathyroidism should be considered to have FMTC. Families with fewer than four affected members or young families without pheochromocytoma or hyperparathyroidism should be considered to have \textit{unclassified} MEN2 and screened as patients with MEN2A until they meet criteria for MEN2A or FMTC. A broad overlap exists in the spectrum of \textit{RET} mutations seen in FMTC and MEN2A, so genetic testing alone cannot always predict MEN2 subtype (Moline & Eng, 2010).

Management and Prophylactic Strategies

MEN2 is caused by mutations in the \textit{RET} proto-oncogene. \textit{RET} mutations cause cells to divide uncontrollably, resulting in tumor formation. Genetic testing can identify \textit{RET} mutations in about 95% of people with clinical symptoms of MEN2A and MEN2B, and in about 88% of families with FMTC. All children of a parent with MEN2 have a 50% chance of inheriting the \textit{RET} mutation and developing the disease. Every patient who has MTC should be assessed for MEN2 because about 25%–30% of the patients have an \textit{RET} mutation. MTC in MEN2 often is the first expressed abnormality. It typically involves both lobes of the thyroid gland and is multicentric, in contrast to MEN2B, which may have an onset in childhood and aggressive MTC.

\section*{Pheochromocytoma}

- A pheochromocytoma is a rare tumor of the adrenal gland that causes an excessive release of epinephrine and norepinephrine.
- Most are benign tumors.
- A pheochromocytoma may develop in one or both adrenal glands.
- The primary symptoms are uncontrolled hypertension, tremor, and sleep disturbances because of the excessive release of epinephrine and norepinephrine.
- The primary management is surgical removal that is attempted after hypertension is controlled with medication.

\section*{Hyperparathyroidism}

- Hyperparathyroidism is excessive production of parathyroid hormone (PTH) by the parathyroid glands.
- PTH triggers the release of too much calcium into the bloodstream.
- Symptoms include back pain, bone pain, decreased height because of osteoporosis, depression, fatigue, increased urine output, increased thirst, urticaria, joint pain, and loss of appetite.
- Primary treatment is surgical removal of the parathyroid gland.

\section*{Hirschsprung Disease}

- Hirschsprung disease occurs when part or all of the large intestine lacks nerve cells, resulting in severe constipation and, sometimes, obstruction.
- Difficulty absorbing nutrients from food often occurs.
- Most cases are diagnosed in infancy.
- Treatment is a surgery called a pull-through procedure where a surgeon removes the segment of the large intestine lacking nerve cells and connects the healthy segment to the anus.
to sporadic MTC, which arises in one lobe (Akerström & Stålberg, 2009).

Genetic testing can both confirm a diagnosis of MEN2 in individual patients and identify family members who may be at risk for developing the disease. Depending on the specific RET mutation, predicting the severity and progression of the disease to some degree is possible. This is helpful in determining screening recommendations as well as the appropriate age for performing a prophylactic thyroidectomy (see Table 2). For example, the specific mutation identified in T.M. is associated with MEN2A, is classified in the intermediate risk category, and is associated with a higher incidence of pheochromocytomas and hyperparathyroidism. Guidelines indicate that people found to have this specific RET mutation should have prophylactic thyroidectomy by age 5 and begin screening for pheochromocytoma and hyperparathyroidism by age 8 (Moline & Eng, 2010).

Surgery is the primary treatment for patients who have confirmed MTC. In addition, all patients who have a germline RET mutation should be referred for surgical intervention, whether or not they have calcitonin elevations. Before proceeding with any surgery, a patient with MTC should be evaluated for a pheochromocytoma. A confirmed pheochromocytoma must be treated first before proceeding with the thyroidectomy (Callender, Rich, & Perrier, 2008).

Almost all patients with MEN2 eventually develop MTC. Early detection is difficult, and the treatment options for locally advanced and metastatic disease are limited. Therefore, patients at risk for inheriting an RET mutation should undergo predictive genetic testing in childhood and gene carriers should undergo prophylactic surgical removal of the thyroid gland. Thyroidectomy during childhood is associated with low morbidity and mortality (Moline & Eng, 2010). Annual measurement of serum calcitonin concentration to detect residual or recurrent MTC after thyroidectomy, even if thyroidectomy was performed prior to biochemical evidence of disease, is recommended (Moline & Eng, 2010).

A pheochromocytoma is diagnosed in about 50% of people with MEN2A and MEN2B, but does not occur in individuals with true FMTC. In individuals with MEN2A, pheochromocytomas occur at an earlier age and are more likely to be bilateral than those that occur as sporadic tumors. Although a pheochromocytoma is a tumor, it rarely is malignant in MEN2. If detected early, pheochromocytomas are easily treated. However, if not treated, they may be fatal because of dangerously high blood pressures that can occur during accidents, surgery, childbirth, or other physically stressful situations. Because pheochromocytomas can be the first symptom of MEN2A, all patients with pheochromocytomas should be assessed for MEN2. Patients who have bilateral pheochromocytomas, as well as young patients who have a unilateral pheochromocytoma, should be referred for genetic evaluation and counseling with consideration for genetic testing (Lindor et al., 2008). Those carrying the MEN2 mutation should have regular screening for pheochromocytoma to facilitate early diagnosis and treatment before the tumor becomes symptomatic. Screening also should be done prior to any elective surgery, pregnancy, and childbirth. Screening involves a 24-hour urine collection that measures levels of catecholamines and metanephrines. If screening indicates a pheochromocytoma, an imaging study will be ordered that may include a computed tomography scan, magnetic resonance imaging, or a special nuclear medicine test called an m-iodobenzylguanidine scan (Richards, 2008). It also has been recommended

### Table 1. Clinical Findings in Multiple Endocrine Neoplasia 2 (MEN2) Subtypes

<table>
<thead>
<tr>
<th>TYPE</th>
<th>SYMPTOMS AND CLINICAL CHARACTERISTICS</th>
<th>% OF SYMPTOM OCCURRENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial medullary thyroid cancer</td>
<td>Medullary thyroid cancer</td>
<td>100</td>
</tr>
<tr>
<td>MEN2A</td>
<td>Medullary thyroid cancer</td>
<td>95–100</td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma</td>
<td>40–50</td>
</tr>
<tr>
<td></td>
<td>Primary hyperparathyroidism</td>
<td>10–30</td>
</tr>
<tr>
<td></td>
<td>Hirschsprung disease</td>
<td>&lt; 1</td>
</tr>
<tr>
<td></td>
<td>Cutaneous lichen amyloidosis</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>MEN2B</td>
<td>Medullary thyroid cancer</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Mucosal-intestinal ganglioneuromas</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Marfanoid habitus</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Mucosal neuromas in the tongue,</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>lips, and eyelids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma</td>
<td>50</td>
</tr>
</tbody>
</table>

*Note. Based on information from Akerström & Stålberg, 2009; Lindor et al., 2008; Richards, 2008.*

### Table 2. Genotype-Phenotype Correlations and Management Recommendations in MEN2

<table>
<thead>
<tr>
<th>MEN2 SUBTYPE</th>
<th>RISK FOR MEDULLARY THYROID CANCER</th>
<th>AGE FOR PROPHYLACTIC THYROIDECTOMY</th>
<th>AGE TO SCREEN FOR PHEOCHROMOCYTOMA AND HYPERPARATHYROIDISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN2A</td>
<td>Lowest risk (level 1)</td>
<td>5–10 years</td>
<td>10–20 years</td>
</tr>
<tr>
<td>MEN2A</td>
<td>Intermediate risk (level 2)</td>
<td>5 years</td>
<td>10–20 years</td>
</tr>
<tr>
<td>MEN2B</td>
<td>Highest risk (level 3)</td>
<td>6 months</td>
<td>6–8 years</td>
</tr>
<tr>
<td>FMTC</td>
<td>Lowest risk (level 1)</td>
<td>5–10 years</td>
<td>Not indicated</td>
</tr>
<tr>
<td>FMTC</td>
<td>Intermediate risk (level 2)</td>
<td>5 years</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

*These guidelines are subject to continued modification as more information becomes available. FMTC—familial medullary thyroid cancer; MEN2—multiple endocrine neoplasia 2

*Note. Based on information from Alevizaki & Stratakis, 2009; American Thyroid Association Guidelines Task Force, 2009; Lindor et al., 2008; Raue & Frank-Raue, 2010.*
that children who have Hirschsprung disease should undergo MEN2 testing (Lindor et al., 2008).

**Conclusion**

This case illustrates the importance of recognizing the clinical manifestations of MEN2. Figure 3 lists key features of MEN2 that serve as indications for referral for an MEN2 genetic evaluation. Knowledge of MEN2 enables oncology nurses to appropriately recognize and refer patients at risk for this disorder for genetic evaluation and testing. This, in turn, allows for early diagnosis and optimal medical management and supportive care for patients and families with MEN2.

Families affected by MEN2 will require extensive lifetime surveillance and, in most cases, major prophylactic surgeries. Healthcare professionals should provide support and encouragement that this is the best approach to prevent or detect disease early and ultimately decrease the morbidity and mortality associated with the MEN2 diagnosis. The lengthy surveillance requires careful coordination so that patients and families are completely clear about what tests will be needed, who will order them and report the results, who will be providing follow-up (a specialist or primary care provider), and what symptoms (particularly those of a pheochromocytoma or hyperparathyroidism) should be reported promptly. For patients undergoing thyroidectomy, lifetime medication and blood monitoring of thyroid hormone levels will be necessary. Patients will need support and encouragement to be compliant with taking the medication and the ongoing monitoring.

Family members will experience fear and anxiety and may be overwhelmed by the diagnosis. Compassionate care combined with honest information that is understandable at age-appropriate levels is important. As time passes, children will need more information to learn to manage the diagnosis as independently as possible. In addition, affected families should be managed by specialists with experience dealing with MEN2. Genetics professionals usually facilitate genetic testing and often coordinate follow-up care. They can assist parents who may experience feelings of guilt if a genetic mutation was passed to their child. People with cancer predisposition syndromes may become preoccupied with the threat of cancer, loss, or disability and experience psychological distress. Encouraging patients to verbalize feelings and concerns is important to facilitate adjustment and manage problems promptly. For those with significant psychosocial distress, a referral to a counselor may be beneficial. Support resources for families and professionals are listed in Figure 4.

**Author Contact:** Suzanne M. Mahon, RN, DNSc, AOCN®, APNG, can be reached at mahonsm@slu.edu, with copy to editor at CJONEditor@ons.org.

**References**


