Multiple Endocrine Neoplasia (MEN) Type 2

WHAT IS THE THYROID GLAND?

The thyroid gland is a butterfly-shaped endocrine gland that is normally located in the lower front of the neck. The thyroid's job is to make thyroid hormones, which are secreted into the blood and then carried to every tissue in the body. Thyroid hormones help the body use energy, stay warm and keep the brain, heart, muscles, and other organs working as they should.

WHAT IS MEN 2?

MEN2 describes a group of disorders that cause one or more glands in the body to develop tumors that produce excess hormones. These conditions usually run in families and can be passed from one generation to the next. There are two types: MEN2A and MEN2B. Individuals with MEN2A can develop medullary thyroid cancer (MTC), primary hyperparathyroidism, and pheochromocytoma (PHEO). Some may also develop a skin condition called cutaneous lichen amyloidosis (CLA) or a bowel condition called Hirschprung disease (HD). Individuals with MEN2B all develop MTC and about half develop PHEO, and they do not get primary hyperparathyroidism. Affected individuals may also have: difficulty making tears, thickened lips, eyelids that turn outward, tall and lanky body type, high-arched feet, and overgrowths (ganglioneuromatosis or neuromas) of mucosal surfaces (especially the tongue) and the gastrointestinal tract/bowel. Individuals commonly have symptoms of constipation or diarrhea due to an abnormally enlarged and poorly working large intestine.

MEDULLARY THYROID CANCER (MTC)

Medullary Thyroid Cancer is a rare tumor of the thyroid gland that comes from cells in the thyroid called parafollicular cells or C-cells. It accounts for 1-2% of thyroid cancers in North America. These cells can produce proteins called "calcitonin" and "carcinoembryonic antigen (CEA)", which can be measured in the blood and help indicate the extent of C-cell growth and/or spread. In MTC, thyroid function tests such as thyroid hormone (T4) and thyroid stimulating hormone (TSH) levels are usually normal. MTC may spread to the lymph nodes or, in more advanced cases, to other areas of the body such as the lungs, liver, and bones.

PHEOCHROMOCYTOMA

A PHEO is a tumor of the adrenal glands, small glands located above the kidneys, that make high levels of catecholamines (epinephrine and norepinephrine; also known as adrenaline and noradrenaline). In MEN2, PHEOs are usually benign and do not spread beyond the adrenal glands. Symptoms of a PHEO may include palpitations, high blood pressure, severe headaches, increased sweatiness and paleness. Testing for PHEO includes collecting a urine sample (generally over a 24-hour period) or a blood sample to check for a metabolized products of catecholamines called metanephrines. High metanephrines are an indicator of a PHEO and require further investigation, usually with a CT scan or MRI.

HYPERPARATHYROIDISM

The four parathyroid glands lie behind the thyroid gland and produce parathyroid hormone (PTH). PTH is responsible for maintaining normal calcium levels in the blood. Overproduction of PTH from benign tumors in the parathyroid glands can lead to high calcium levels. Symptoms may include irritability, kidney stones, constipation, increased urination, and osteoporosis (low bone strength) leading to broken bones.

CUTANEOUS LICHEN AMYLOIDOSIS (CLA)

This is a rare disorder with symptoms of skin darkening and itchy areas, typically on or between the shoulder blades. The itchiness may worsen with stress and improve with sun exposure. This area may become darkened with scratching. This symptom may start before a diagnosis of MTC.

HIRSCHPRUNG DISEASE (HD)

HD results from an undergrowth of nerve cells in the bowel. As a result, the muscles in the intestinal wall cannot contract and relax adequately, and affected individuals with HD have difficulty passing stools. This usually presents in infancy or early childhood.

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WHAT IS THE *RET* MUTATION?

The *RET* gene is found in the DNA of all cells in the body. A DNA change (also known as a mutation) in one of the two copies of the *RET* gene is responsible for MEN2 and may be passed on from parent to child (autosomal dominant inheritance pattern). Since the discovery of the *RET* gene as the cause of MEN2 in 1993, numerous different DNA changes have been identified. It is important to know what particular change runs in your family, as the specific DNA change determines the likelihood and timing of developing MTC. Risks for developing the other associated MEN2 conditions are also related to the specific *RET* mutation.

WHO SHOULD HAVE *RET* TESTING?

Genetic counseling and testing for *RET* gene changes should be offered to all individuals diagnosed with MTC or CLA as well as the first-degree relatives (parents, siblings and children) of all individuals with a known inherited *RET* gene change. This *RET* testing also can be considered in some patients with PHEO and primary hyperparathyroidism. In addition, primary hyperparathyroidism at a young age also should prompt testing.

HOW DOES MY MEN2 PHYSICIAN FOLLOW MY CONDITION?

There is currently no way to alter the DNA change that causes MEN2. Instead, medical care for carriers of a *RET* gene change is focused on identifying the conditions associated with MEN2 at an early stage and/or intervening *before* a significant problem develops. This is often referred to as "*pre-symptomatic*" screening.

Clinicians use several approaches in pre-symptomatic screening for MEN2-associated conditions:

HYPERPARATHYROIDISM

- Blood tests for calcium with or without PTH levels

MEDULLARY THYROID CANCER

For people with MEN2, blood tests for calcitonin are checked to identify the appropriate time to undergo surgery.

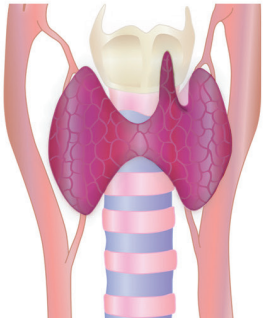
- For individuals who have already undergone surgery, calcitonin and CEA levels are used to monitor for recurrence of MTC.
- Ultrasound scans of the neck and CT/MRI of the neck, chest, and abdomen/pelvis also may be used prior to any surgery and following surgery to identify tumors.

PHEOCHROMOCYTOMA

- Blood or urine tests may be used to identify high levels of metanephrines.
- If metanephrine levels are high, CT scan or MRI of the abdomen may be used to assess the adrenal glands.

The timing of when to start surveillance, and how often to do each of these tests, depends on the specific gene change carried by a person with MEN2. According to the risk of developing MTC, each DNA change is categorized as "moderate", "high" or "highest" risk. The specific risk category guides screening. For children with "high" or "highest" risk gene changes, thyroid surgery is currently recommended at a young age to avoid the development or spread of MTC.

In the "highest" risk group, which includes only those children with MEN2B, surgery to remove the thyroid gland is recommended before 1 year of age. In the "high" risk group, removal of the thyroid gland is recommended before age 5. Blood tests to look for PHEO begins at age 11 and, in MEN2A only, tests to look for hyperparathyroidism also start at age 11. In children with a "moderate" risk DNA change, surgery to remove the thyroid gland is considered when the calcitonin levels start to rise and tests for PHEO and hyperparathyroidism begin at age 16 years.



FURTHER INFORMATION

Further details on this and other thyroid-related topics are available in the patient thyroid information section on the American Thyroid Association® website at *www.thyroid.org*.

For information on thyroid patient support organizations, please visit the *Patient Support Links* section on the ATA website at *www.thyroid.org*

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HOW ARE MEN2 CONDITIONS TREATED?

MEDULLARY THYROID CANCER

MTC is typically treated with surgery to remove the entire thyroid gland and neck lymph nodes. In children known to have an inherited *RET* gene change, thyroid removal is recommended before MTC develops or has had a chance to spread. Removal of lymph nodes is often not necessary in children when surgery is performed by the recommended age unless calcitonin levels are very high. If there is MTC remaining after initial surgery, some patients require additional surgery, or other treatments to control the disease or symptoms if MTC has spread to areas outside of the neck.

PHEOCHROMOCYTOMA

PHEO is treated by removing the affected adrenal gland, an operation called “adrenalectomy”. Since there are two adrenal glands, one affected gland can be safely removed without affecting adrenal gland function. In MEN2, there is a risk that PHEO may occur in both adrenal glands, or may already have developed in both. Because of this a “cortical-sparing adrenalectomy” may be performed, which is an operation that does not remove all of the adrenal glands to preserve some of the adrenal gland function. Some patients may require steroid hormones post-operatively if both adrenal glands require surgery.

PARATHYROID HYPERPLASIA

For patients who develop high calcium levels and/or symptoms of hyperparathyroidism (*see above*), one or more parathyroid glands may be removed. The specific procedure may vary and should be discussed with the surgeon. If hyperparathyroidism persists after surgery, either an additional surgery or medications may be advised.

CUTANEOUS LICHEN AMYLOIDOSIS (CLA)

A dermatologist would help to treat CLA, and moisturizing lotions, steroid creams and/or antihistamines may be used. Since scratching can make CLA worse, adequate treatment of the itching is important to minimize the extent of the disease.

HIRSCHSPRUNG DISEASE

Consultation with a pediatric surgeon is necessary if a child is symptomatic. Depending on the severity of the condition, both surgical and non-surgical options may be considered.

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