CONDITION

Multiple endocrine neoplasia (MEN) II

Multiple endocrine neoplasia type 2 is an inherited condition that raises the risk of tumors in several hormone-producing glands.

WHAT IT IS
Inherited condition causing tumors in hormone-producing glands

BODY SYSTEM
Hormone system, especially thyroid, adrenal, and parathyroid glands

MAIN SYMPTOMS
Thyroid lump, headaches, sweating, racing heartbeat

WHAT CAUSES IT
Inherited RET gene variant

HOW IT IS DIAGNOSED
RET genetic testing

MAIN TREATMENT
Surgery, hormone replacement, and lifelong monitoring

CAN IT BE CURED?
No - inherited RET variant remains lifelong

IS IT AN EMERGENCY?
Sometimes - severe headache, chest pain, racing heartbeat

LONG-TERM OUTLOOK
Often manageable with early treatment and lifelong surveillance

Overview

Multiple endocrine neoplasia type 2, usually called MEN2, is an inherited condition that increases the chance of developing tumors in certain glands. These glands make hormones, which are chemical messengers that control many body functions.

MEN2 most often affects the thyroid, adrenal, and parathyroid glands. Its main concern is medullary thyroid cancer, a cancer that begins in thyroid cells called C cells. These cells make the hormone calcitonin.

There are two main forms:

Some families mainly develop medullary thyroid cancer without the other typical tumors. This has sometimes been called familial medullary thyroid cancer, although it is generally

considered part of the MEN2 spectrum.

MEN2 matters because tumors can begin before symptoms appear. Genetic testing and regular screening may find risks early enough for preventive surgery or prompt treatment.

- MEN2A can cause medullary thyroid cancer, adrenal gland tumors called pheochromocytomas, and overactive parathyroid glands.
- MEN2B can cause medullary thyroid cancer and pheochromocytomas. It may also cause nerve growths on the lips or tongue, digestive problems, and a tall, slender body shape.

Symptoms

MEN2 does not always cause noticeable symptoms at first. Some people learn that they have it through genetic testing after a relative is diagnosed.

Symptoms depend on which glands are affected.

Medullary thyroid cancer may cause:

A pheochromocytoma develops in an adrenal gland, located above a kidney. It can release large amounts of hormones such as adrenaline. Symptoms may come in sudden episodes and include pounding headaches, heavy sweating, a fast or forceful heartbeat, shaking, anxiety, and high blood pressure. Some tumors are found during screening before symptoms develop.

Overactive parathyroid glands produce too much parathyroid hormone, raising calcium in the blood. This occurs mainly in MEN2A. It may cause no symptoms, or it may lead to thirst, frequent urination, constipation, fatigue, muscle weakness, kidney stones, or bone loss.

MEN2B can cause small, soft nerve growths called mucosal neuromas. These are often visible on the lips or tongue. The lips may appear full, and the eyelids may turn outward. Nerve changes in the digestive tract can cause constipation, diarrhea, abdominal swelling, or feeding problems beginning in infancy or childhood.

- A lump or swelling in the front of the neck
- Enlarged lymph nodes in the neck
- A hoarse voice or trouble swallowing
- Persistent diarrhea in some people with advanced cancer

Causes and risk factors

MEN2 is caused by a harmful change, also called a pathogenic variant, in the RET gene. RET

helps control cell growth. Certain changes keep the gene switched on, allowing some hormone-producing cells to grow into tumors.

The condition follows an autosomal dominant inheritance pattern. This means a person with a RET variant has a 1 in 2 chance of passing it to each child. The chance is the same for every pregnancy.

Not everyone inherits the variant from a parent. New, or de novo, RET variants can occur for the first time in one person. This is especially common in MEN2B. That person can still pass the variant to their children.

The specific RET variant helps estimate which tumors are more likely and how early medullary thyroid cancer may develop. It also helps specialists plan the timing of screening and preventive thyroid surgery.

MEN2 is not caused by diet, stress, alcohol, or something a parent did during pregnancy.

Diagnosis

A germline RET genetic test confirms MEN2. "Germline" means the variant is present throughout the body and can be inherited. Testing is usually done using blood or saliva.

Genetic counseling is important before and after testing. A genetic counselor can explain possible results, what they may mean for relatives, and how genetic information may affect future family planning.

If a RET variant is found, tests are used to look for tumors and hormone changes. These may include:

Metanephrines are substances produced when the body breaks down adrenaline-like hormones. High levels can suggest a pheochromocytoma. Imaging such as CT or MRI may then be used to locate the tumor.

A thyroid nodule may also be assessed with ultrasound and a fine-needle biopsy, in which a thin needle removes cells for examination. However, people from a family with MEN2 should generally be offered RET testing even if they have no thyroid lump.

When one person is diagnosed, close biological relatives may be offered targeted testing for the same family variant. A negative targeted test usually means that relative did not inherit the family's MEN2 risk.

- Blood calcitonin testing and a neck ultrasound for medullary thyroid cancer
- Blood or 24-hour urine metanephrine tests for pheochromocytoma

- Blood calcium and parathyroid hormone tests for overactive parathyroid glands

Treatment and management

Care is usually coordinated by specialists in endocrinology, genetics, thyroid surgery, adrenal surgery, and cancer care. Treatment is based on the RET variant, test results, age, and which glands are affected.

Removing the thyroid before cancer develops can prevent medullary thyroid cancer. The timing is not the same for everyone. Some higher-risk RET variants require surgery in early childhood, while other variants allow more time for monitoring. The decision should be made by an experienced MEN2 team.

If medullary thyroid cancer is already present, treatment usually includes complete removal of the thyroid. Nearby lymph nodes may also need to be removed. After thyroid removal, lifelong thyroid hormone replacement is required.

Advanced medullary thyroid cancer may be treated with medicines that block signals driving cancer growth. Some medicines specifically target abnormal RET activity. These treatments can control cancer for some people but do not remove the inherited variant.

Pheochromocytomas are usually treated with adrenal surgery. Medicines are given before surgery to control the effects of excess adrenal hormones. In some cases, surgeons can preserve part of the adrenal gland to reduce the chance of lifelong adrenal hormone replacement.

A pheochromocytoma must be considered before thyroid or parathyroid surgery. An undetected tumor can release a dangerous surge of hormones during an operation or other major physical stress.

Overactive parathyroid glands may be monitored or treated with surgery, depending on calcium levels, symptoms, kidney health, and bone health.

Regular follow-up continues after treatment because additional tumors can develop, and treated tumors can sometimes return.

Complications

Medullary thyroid cancer can spread to lymph nodes, the lungs, liver, or bones. The chance of spread is lower when thyroid surgery happens before cancer develops or while it remains confined to the thyroid.

A pheochromocytoma can cause severe blood pressure changes, abnormal heart rhythms, stroke, heart injury, or a hormone crisis. These complications are uncommon with appropriate detection and preparation for surgery.

Long-term high calcium from overactive parathyroid glands can contribute to kidney stones, reduced kidney function, and weaker bones.

Treatment can also have lasting effects. Thyroid surgery may affect the voice or lower calcium if the parathyroid glands are injured. Removing both adrenal glands causes adrenal insufficiency, meaning the body cannot make enough essential adrenal hormones. This requires lifelong replacement medicine and an emergency plan for illness or injury.

Prevention

The inherited RET variant itself cannot currently be prevented or removed.

Many serious effects of MEN2 can be prevented or reduced. Predictive genetic testing can identify relatives who need screening. For people at risk of medullary thyroid cancer, thyroid removal at the recommended time may prevent the cancer from developing.

Regular blood tests and imaging can help detect pheochromocytoma or parathyroid problems before major complications occur.

People considering pregnancy can discuss reproductive options with a genetics professional. Options may include testing during pregnancy or in vitro fertilization with testing of embryos. These are personal choices, not requirements.

Living with it and what to expect

MEN2 is lifelong, even after affected glands or tumors are removed. Follow-up usually continues every year, although the schedule may be more frequent around diagnosis, surgery, or an abnormal test.

Over months and years, monitoring may include calcitonin, adrenal hormone tests, calcium measurements, and imaging when needed. The exact plan is guided by the RET variant and previous treatment.

Many people continue their usual education, work, exercise, and family life. Daily treatment may be limited to thyroid hormone replacement. People who have had both adrenal glands removed need additional daily medicines and must be prepared to manage adrenal insufficiency during illness.

The outlook is strongly linked to when medullary thyroid cancer is found and whether it has spread. Early preventive treatment can substantially reduce its impact. Pheochromocytomas and parathyroid problems are often treatable, but they may develop later or recur.

MEN2 can also affect emotional well-being. Testing relatives, making decisions for children, or living with repeated screening may cause worry. Genetics teams, specialist nurses, counselors, and patient support groups can help with these concerns.

Keep a clear record of your RET variant, operations, medicines, and follow-up results. Tell healthcare professionals about MEN2 before surgery, pregnancy care, or procedures requiring anesthesia.

When to get medical help

Arrange routine medical follow-up if you have a RET variant, even when you feel well. Contact your MEN2 team if you develop a new neck lump, ongoing hoarseness, trouble swallowing, repeated headaches with sweating or palpitations, kidney stone symptoms, or persistent digestive changes.

Seek urgent medical care for repeated episodes of severe headache, pounding heartbeat, sweating, or very high blood pressure. These can be signs of a pheochromocytoma releasing excess hormones.

Call emergency services for chest pain, severe shortness of breath, fainting, new weakness on one side, confusion, or a severe headache with a racing heartbeat and sweating.

If you have adrenal insufficiency, follow your emergency plan during vomiting, serious illness, injury, or an adrenal crisis. Severe weakness, repeated vomiting, fainting, confusion, or inability to keep replacement medicine down requires emergency care.

Common questions

Is MEN2 the same as thyroid cancer?

No. MEN2 is an inherited condition that raises the risk of several tumors. Medullary thyroid cancer is its most consistent feature, but adrenal and parathyroid glands may also be affected.

Does everyone with MEN2 develop cancer?

The risk of medullary thyroid cancer is very high, but the timing and behavior of the cancer differ by RET variant. Not everyone develops every MEN2-related tumor.

Can MEN2 skip a generation?

A person who does not inherit the family's RET variant cannot pass that variant to their children. MEN2 may appear to skip a generation if relatives were never tested, had few symptoms, or died before a tumor was recognized.

Does removing the thyroid cure MEN2?

Removing the thyroid can prevent or treat medullary thyroid cancer, but it does not remove the RET variant. Screening for adrenal and, in MEN2A, parathyroid tumors must continue.

What is the difference between MEN1 and MEN2?

They are separate inherited conditions caused by different genes. MEN1 more often affects the parathyroid, pituitary, and pancreas. MEN2 is linked to RET and mainly affects the thyroid, adrenal, and parathyroid glands.

Should my children be tested?

Children of a person with a harmful RET variant may be offered targeted genetic testing. Testing can be time-sensitive because some variants require thyroid assessment and treatment during childhood. A genetics and pediatric endocrine team can guide the process.

Sources

- National Cancer Institute. Genetics of Endocrine and Neuroendocrine Neoplasias (PDQ): Multiple Endocrine Neoplasia Type 2 . NCI Cancer Information Summaries.
- Wells SA Jr, Asa SL, Dralle H, and colleagues. "Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma." Thyroid . 2015;25(6):567-610.
- Multiple Endocrine Neoplasia Type 2 . GeneReviews. University of Washington, Seattle; NCBI Bookshelf.
- Lenders JWM, Duh QY, Eisenhofer G, and colleagues. "Pheochromocytoma and Paraganglioma: An Endocrine Society Clinical Practice Guideline." Journal of Clinical Endocrinology and Metabolism . 2014;99(6):1915-1942.