Multiple Endocrine Neoplasia Type 1

National Endocrine and Metabolic Diseases Information Service

U.S. Department of Health and Human Services

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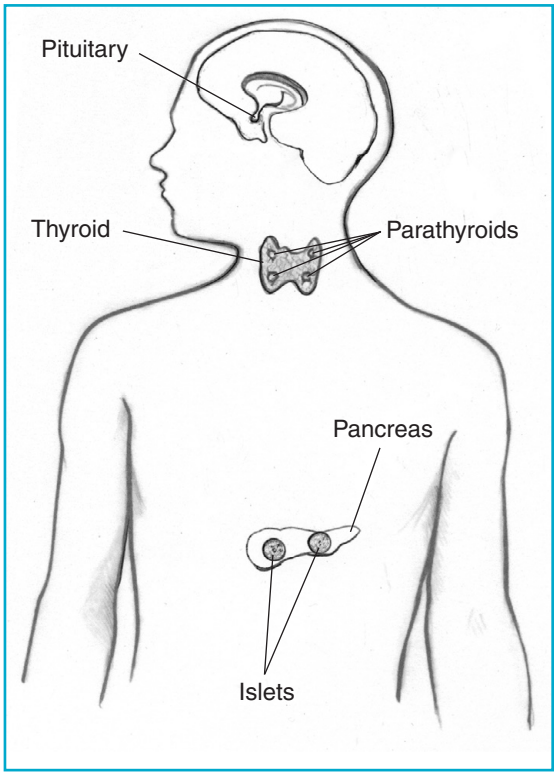
What is multiple endocrine neoplasia type 1 (MEN1)?

MEN1 is an inherited disorder that causes tumors in the endocrine glands and the duodenum, the first part of the small intestine. MEN1 is sometimes called multiple endocrine adenomatosis or Wermer's syndrome, after one of the first doctors to recognize it. MEN1 is rare, occurring in about one in 30,000 people.[1] The disorder affects both sexes equally and shows no geographical, racial, or ethnic preferences.

Endocrine glands release hormones into the bloodstream. Hormones are powerful chemicals that travel through the blood, controlling and instructing the functions of various organs. Normally, the hormones released by endocrine glands are carefully balanced to meet the body's needs.

In people with MEN1, multiple endocrine glands form tumors and become hormonally overactive, often at the same time. The overactive glands may include the parathyroids, pancreas, or pituitary. Most people who develop overactivity of only one endocrine gland do not have MEN1.



In MEN1, the overactive glands may include the parathyroids, pancreas, or pituitary.

[1]White ML, Doherty GM. Multiple endocrine neoplasia. *Surgical Oncology Clinics of North America.* 2008;17:439–459.

How does MEN1 affect the endocrine glands and the duodenum?

The Parathyroid Glands

The parathyroids are the endocrine glands earliest and most often affected by MEN1. The body normally has four parathyroid glands, which are located close to the thyroid gland in the front of the neck. The parathyroids release into the bloodstream a chemical called parathyroid hormone (PTH), which helps maintain a normal supply of calcium in the blood, bones, and urine.

Hyperparathyroidism

In MEN1, all four parathyroid glands tend to be overactive, causing hyperparathyroidism. The parathyroid glands form tumors that release too much PTH, leading to excess calcium in the blood. High blood calcium, known as hypercalcemia, can exist for many years before it is found by accident or through screening for MEN1. Unrecognized hypercalcemia can cause excess calcium to spill into the urine, leading to kidney stones or kidney damage. Also, the bones may lose calcium and weaken.

Nearly everyone who inherits a susceptibility to MEN1 will develop hyperparathyroidism by age 50, but the disorder can often be detected before age 20. Hyperparathyroidism may cause no problems for many years, or it may cause tiredness, weakness, muscle or bone pain, constipation, indigestion, kidney stones, or thinning of bones.

Doctors must decide whether hyperparathyroidism in MEN1 is severe enough to need treatment, especially in a person who has no symptoms. The usual treatment is an operation to remove most or all of the parathyroid glands. One option is to remove the three largest glands and all but a small part of the fourth. Another is to remove all four glands and at the same time transplant a small part of one gland into the forearm. By maintaining a portion of one gland, the parathyroid transplant continues to release PTH into the bloodstream to do its job.

After parathyroid surgery, regular testing of blood calcium should continue because often the small piece of remaining parathyroid tissue grows larger and causes recurrent hyperparathyroidism. If the remaining piece is in the forearm and additional surgery is needed to remove more parathyroid tissue, the arm operation can be performed under local anesthesia.

Sometimes all four glands are completely removed to prevent recurrence or may be unintentionally removed during parathyroid surgery. People whose parathyroid glands have been completely removed must take daily supplements of calcium and vitamin D or another related treatment to prevent hypocalcemia, or low blood calcium.

The Pancreas and Duodenum

Located behind the stomach, the pancreas has two major roles: to release digestive juices into the intestines and key hormones into the bloodstream. The duodenum is the first part of the small intestine next to the pancreas. The pancreatic hormones are normally produced by small clusters of specialized cells called pancreatic islets. Some of the major hormones produced by the pancreatic islets are

- insulin—lowers blood glucose, also called blood sugar
- glucagon—raises blood glucose
- somatostatin—inhibits secretion of certain other hormones
- vasoactive intestinal peptide (VIP)—causes intestinal cells to secrete water into the intestine
- gastrin—causes the stomach to produce acid for digestion

Gastrinomas

In MEN1, gastrin may be oversecreted by tumors called gastrinomas in the pancreas, duodenum, and lymph glands. If exposed to too much gastrin, the stomach releases excess acid, leading to the formation of severe ulcers in the stomach and small intestine. In addition, too much gastrin usually causes serious diarrhea.

People with MEN1 have about a 20 to 60 percent chance of developing gastrinomas.[2] The illness associated with these tumors is called Zollinger-Ellison syndrome. The ulcers caused by untreated gastrinomas are much more dangerous than typical stomach or intestinal ulcers. Left untreated, they can cause rupture of the stomach or intestine and even death.

The gastrinomas associated with MEN1 are not easily cured through tumor surgery because finding the many small gastrinomas in the pancreas, duodenum, and lymph glands is difficult. The mainstay of treatment is powerful medicines called acid pump inhibitors that block stomach acid release. Taken by mouth, these medicines have proven effective in controlling the complications of excess gastrin in most cases of Zollinger-Ellison syndrome.

Rare Pancreatic Complications

Occasionally, a person who has MEN1 develops an islet tumor of the pancreas that secretes high levels of hormones. Insulinomas, for example, produce too much insulin, causing hypoglycemia, or low blood glucose. About 10 percent of adults with MEN1 develop insulinomas.[3] Rare pancreatic tumors may secrete too much glucagon, which can cause diabetes, or too much VIP, which can cause watery diarrhea. Tumors that secrete adrenocorticotropin (ACTH) may also arise in the pancreas. ACTH is normally secreted by the pituitary gland and stimulates the adrenal glands to produce cortisol, a hormone that helps the body respond to stress. Tumors in the pancreas may also infrequently secrete gonadotropin-releasing hormone (GnRH). GnRH is normally secreted by the hypothalamus and stimulates the pituitary gland to release follicle stimulating hormone (FSH), which regulates fertility in men through sperm production and in women through ovulation. In general, surgery is the mainstay of treatment for these uncommon types of tumors.

[2]Jensen RT. Management of the Zollinger-Ellison syndrome in patients with multiple endocrine neoplasia type 1. *Journal of Internal Medicine.* 1998;243(6):477–488.

[3]Larsen PR, Kronenberg HM, Melmed S, Polonsky KS, eds. *Williams Textbook of Endocrinology.* 10th ed. Philadelphia: Saunders; 2003.

The Pituitary Gland

The pituitary, a small gland located at the base of the brain, produces many important hormones that regulate basic body functions. The normal major pituitary hormones are

- prolactin—controls the formation of breast milk and influences fertility and bone strength
- growth hormone—regulates body growth, especially during adolescence
- ACTH—stimulates the adrenal glands to produce cortisol
- thyrotropin—stimulates the thyroid gland to produce thyroid hormones, which regulate metabolism
- luteinizing hormone—stimulates the ovaries or testes to produce sex hormones
- FSH—regulates fertility

Prolactinomas

The pituitary gland becomes overactive in about one in four people with MEN1.[4] This overactivity can usually be traced to a small tumor in the gland that releases too much prolactin, called a prolactinoma. High prolactin levels can cause excessive production of breast milk or interfere with fertility in women or with sex drive and fertility in men. Treatment may not be needed for prolactinomas. If treatment is needed, a medicine known as a dopamine agonist can effectively shrink the tumor and lower the production of prolactin. Occasionally, prolactinomas do not respond well to this medication. In such cases, surgery, radiation, or both may be needed.

Rare Pituitary Complications

Rarely, MEN1 creates pituitary tumors that release high amounts of ACTH, which in turn stimulates the adrenal glands to produce excess cortisol. Too much cortisol can lead to muscle weakness, weakened bones and fractures, and thinning skin, among other problems. Pituitary tumors that produce growth hormone cause excessive bone growth or disfigurement. In general, surgery is the mainstay of treatment for these uncommon types of tumors.

[4]Gardner DG, Shoback D, eds. *Greenspan's Basic & Clinical Endocrinology.* 8th ed. New York: McGraw-Hill; 2007.

Are the tumors associated with MEN1 cancerous?

The tumors associated with MEN1 are usually benign, meaning they are not cancerous. However, they can disrupt normal function by releasing hormones or by crowding nearby tissue. For example, a prolactinoma may become quite large in someone with MEN1. As it grows, the tumor can press against and damage the normal part of the pituitary gland or the nerves for vision. Sometimes impaired vision is the first sign of a pituitary tumor in a person with MEN1.

Another type of benign tumor seen in about one-third of people with MEN1 is a plum-sized, fatty tumor called a lipoma, which grows under the skin. Lipomas cause no health problems and can be removed by simple cosmetic surgery if desired.

Benign tumors do not spread to or invade other parts of the body. Cancer cells, by contrast, break away from the primary tumor and spread, or metastasize, to other parts of the body through the bloodstream or lymphatic system. The pancreatic islet tumors associated with MEN1 tend to be numerous and small, but most are benign and do not release active hormones into the blood. Over time, gastrinomas may become cancerous but are usually slow-growing.

Eventually, about half of people with MEN1 will develop a cancerous pancreatic or carcinoid tumor. A carcinoid is a slow-growing endocrine tumor inside the chest or stomach of a person with MEN1. Although carcinoids arise from endocrine cells, which are present in many parts of the body, they rarely secrete a hormone in a person with MEN1. Carcinoids of the stomach usually do not require treatment.

Treatment of Pancreatic Endocrine Cancer in MEN1

Because the type of pancreatic endocrine cancer associated with MEN1 can be difficult to recognize, difficult to treat, and slow to progress, doctors have different views about the value of surgery in managing these tumors.

One approach is to "watch and wait," using medical, or nonsurgical, treatments. According to this school of thought, pancreatic surgery has serious complications, so it should not be attempted unless it will cure a tumor or cure a hormone excess state.

Another school advocates early surgery, perhaps when a tumor grows to a certain size, to prevent or treat pancreatic endocrine cancer—even if the tumor does not over secrete a hormone—before the cancer spreads. No clear evidence exists, however, that surgery to prevent pancreatic endocrine cancer from spreading actually leads to longer survival for patients with MEN1.

Doctors agree that excessive release of certain hormones—mainly gastrin—from pancreatic endocrine cancer in MEN1 needs to be treated, and medications are often effective in blocking the effects of these hormones. Some tumors, such as insulinomas, are usually benign and single and are curable by pancreatic surgery. Such surgery needs to be considered carefully in each patient's case.

Is MEN1 the same in everyone?

Although MEN1 tends to follow certain patterns, it can affect a person's health in many different ways. Not only do the tumors of MEN1 vary among members of the same family, but some families with MEN1 tend to have a higher rate of prolactin-secreting pituitary tumors and a much lower frequency of gastrin-secreting tumors.

The age at which MEN1 can begin to cause endocrine gland overactivity can differ strikingly from one family member to another. One person may have only mild hyperparathyroidism beginning at age 50, while a relative may develop complications from tumors of the parathyroid, pancreas, and pituitary by age 18.

How is MEN1 detected?

MEN1 is detected by gene testing or, when gene testing is unavailable or yields a negative result, by laboratory tests that measure hormone levels. Less often, MEN1 is diagnosed based on an individual's medical and family history.

The Genetics of MEN1 and MEN1 Carriers

In a person wth MEN1, a mutation, or mistake, exists in the *MEN1* gene in every cell in the person's body. Many different *MEN1* gene mutations have been identified. Each of these mutations can cause the same spectrum of MEN1 tumors. The particular *MEN1* mutation in a person's body may be silent, meaning the person has no symptoms, as in a newborn. Or, the *MEN1* mutation may be expressed as the MEN1 syndrome. A person with a MEN1 mutation, whether showing symptoms or not, is termed a carrier of the *MEN1* mutation or a carrier of the MEN1 syndrome.

MEN1 is an autosomal dominant gene, which means it is inherited by a child from one parent who has the *MEN1* mutation.

Gene Testing

Gene testing can identify whether a person is a carrier of the *MEN1* mutation. Once identified, carriers undergo approximately yearly testing, a process called screening, for biochemical indications of a developing tumor. Relatives who are found to lack the known *MEN1* mutation in their family can be freed from screening for MEN1. A limited number of laboratories in the United States offer *MEN1* gene testing to locate and identify *MEN1* mutations. The gene tests are expensive and can be time-consuming. Once a specific mutation is found in an individual, the gene test for relatives is easier and less expensive.

In 10 to 30 percent of families with MEN1, no mutation is found.[5] However, an undetected *MEN1* mutation may still be likely. Sometimes a person with MEN1 knows of no other case of MEN1 among relatives. The most common explanation is that knowledge of the family's health history is incomplete. Less often, the person carries a new *MEN1* gene mutation.

Gene testing may be offered to people who

- meet the clinical criteria for MEN1 by having at least two of the following: enlarged parathyroid glands, a pancreatic or duodenal endocrine tumor, or a pituitary tumor
- don't meet the clinical criteria but are suspected of having MEN1—for example, those who have multiple parathyroid tumors before age 30
- are first-degree relatives of people with MEN1—children, brothers, or sisters—giving them a 50 percent chance of having inherited the mutation

The Role of Genetic Counseling

Genetic counseling can assist family members in understanding how the test results may affect them individually and as a family. Genetic counseling may include a review and discussion of the psychosocial benefits and risks of genetic testing. Genetic testing results can affect self-image, self-esteem, and individual and family identity. In genetic counseling, issues related to how and with whom genetic test results will be shared and their possible effect on important matters such as health and life insurance coverage can be addressed. These discussions may occur when a family member is deciding whether to proceed with gene testing and again later when the test results are available. A doctor, nurse, or genetics professional provides the genetic counseling.

[5]Ozawa A, Agarwal SK, Mateo CM, et al. The parathyroid/pituitary variant of MEN1 usually has causes other than *p27*Kip1 mutations. *The Journal of Clinical Endocrinology & Metabolism.* 2007;92:1948–1951.

Laboratory Tests

Laboratory tests may be performed periodically to screen for MEN1 tumors. Screening can catch tumors in their early stages of development, detect tumors that have come back, and indicate how large they are and where they are located. Catching tumor development early allows doctors to take steps to prevent serious complications from occurring in people with MEN1. Types of tests used for tumor screening can include

- blood tests—for example, to measure insulin or PTH to detect excess hormone production by a MEN1 tumor.
- other biochemical tests—for example, to measure urinary calcium to detect the results of excess hormone production.
- immunoradiometric assays, a type of blood test—for example, to measure PTH to detect parathyroid tumors.
- imaging tests—for example, ultrasound, computerized tomography (CT), and magnetic resonance imaging (MRI) to allow the doctor to detect tumors that are not secreting hormones. Because imaging tests are more expensive, they are typically done less often than blood tests.

The types of tests performed depend on the purpose of the screening. Periodic screening for MEN1 tumors can have two different purposes:

- **To recognize possible carriers of *MEN1*.** First, screening may be performed to determine if an individual is a carrier of the *MEN1* mutation. This screening includes close relatives of a person known to carry *MEN1*. Although gene testing is one way to identify a carrier of *MEN1*, sometimes these other methods are used due to a lack of resources, or when the underlying mutation cannot be identified. For this screening purpose, tests are directed at tumors that are most frequent and develop the earliest. Examples of these tests include PTH, calcium, and prolactin tests.
- **To detect early tumors in known carriers of *MEN1*.** Second, screening may be performed in known carriers of *MEN1* to look for any tumor that could develop as a result of the mutation. This periodic testing can recognize a tumor early to optimize its treatment. When an individual is a known carrier of *MEN1*, more detailed testing is performed to screen for some of the less likely but still harmful tumors.

Laboratory tests for MEN1 tumors can be repeated yearly without waiting for symptoms to appear. This testing can begin at age 5. In known carriers, imaging tests may be performed every 3 years to locate tumors that cannot be found with other laboratory testing.

If an individual's tests are normal, periodic tumor testing should continue indefinitely. However, an unproven carrier with normal tests beyond age 50 is unlikely to have inherited a *MEN1* gene mutation.

Can MEN1 be cured?

MEN1 cannot be cured, but regular testing can detect many of the problems caused by MEN1 tumors many years before serious complications develop. Finding these tumors early enables doctors to begin preventive treatment, reducing the chances that MEN1 will cause problems later.

Even after treatment, residual tissue can grow back or different glands may become affected. Periodic and careful monitoring enables doctors to adjust an individual's treatment as needed and to check for any new problems caused by MEN1. Most people with MEN1 have a long and productive life.

Should a person who has MEN1 avoid having children?

A person who has MEN1 or who has a *MEN1* gene mutation may have a hard time deciding whether to have a child. Some facts to consider include the following:

- A man or a woman with MEN1 has a 50–50 risk with each pregnancy of having a child with MEN1.
- MEN1 tends to fit a broad pattern within a given family, but the severity of the disorder varies widely from one family member to another. In particular, a parent's experience with MEN1 cannot be used to predict the eventual severity of MEN1 in a child.
- The tumors that result from MEN1 do not usually develop until adulthood. Treatment may require regular monitoring and considerable expense, but the disease usually does not prevent an active, productive adulthood.
- Prolactin-releasing tumors in a man or woman with MEN1 may inhibit fertility and make it difficult to conceive.
- Hyperparathyroidism during pregnancy may raise the risks of complications for mother and child.
- Pregnancy is usually normal for the mother or child who is a carrier of *MEN1*.

Genetic counselors and other professionals can provide information to help with the decision-making process, but they will not tell individuals or couples what decision to make or how to make it.

Points to Remember

- Multiple endocrine neoplasia type 1 (MEN1) is an inherited disorder that causes hormone-secreting tumors in the duodenum and the endocrine glands—most often the parathyroid, pancreas, and pituitary.
- Overactive parathyroid glands can lead to tiredness, weakness, muscle or bone pain, constipation, indigestion, kidney stones, or thinning of bones.
- Pancreatic and duodenal endocrine tumors called gastrinomas can cause dangerous stomach or intestinal ulcers.
- Pituitary tumors called prolactinomas can cause excessive production of breast milk or interfere with fertility in women or with sex drive and fertility in men.
- Although many tumors associated with MEN1 are benign, about half of people with MEN1 will eventually develop a cancerous tumor.
- *MEN1* carriers can be detected through gene testing or other laboratory tests.
- MEN1 cannot be cured, but regular testing can detect the problems caused by MEN1 tumors many years before serious complications develop. Careful monitoring enables doctors to adjust an individual's treatment as needed.

Hope through Research

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and other Institutes of the National Institutes of Health conduct and support research in endocrine disorders, including MEN1. Researchers are conducting genetic studies to better understand *MEN1* gene mutations and their effects. Other studies are examining new drug treatments for hyperparathyroidism, carcinoid tumors, and pancreatic islet tumors. The psychosocial aspects of MEN1 are also under investigation.

Participants in clinical trials can play a more active role in their own health care, gain access to new research treatments before they are widely available, and help others by contributing to medical research. For information about current studies, visit *www.ClinicalTrials.gov.*

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