What Is Multiple Endocrine Neoplasia Type 1 (MEN1)?

Multiple endocrine neoplasia type 1 (MEN1) is a condition that can be passed down in families. MEN1 causes more than one *gland* of the body's *endocrine system* to develop tumors, including some *neuroendocrine tumors* (NETs). The affected glands may then make greater than normal amounts of *hormones*, the body's chemical messengers, which in turn cause a range of different symptoms. Each type of growth may occur alone and separate from MEN.

Multiple = more than one

Endocrine = gland system

Neoplasia = increase in growth of normal cells to form a tumour

How is MEN1 diagnosed?

A person is said to have MEN1 if they have:

1. 2 or more tumors that occur in MEN1; or
2. Only one tumor, but there is a family history of relatives with MEN1; or
3. A blood test that shows a change in a *gene that is known to cause MEN1*

A patient may have a gene change that causes MEN1, but not have developed any of the tumors. This patient is at risk of developing MEN1 tumors and should be offered regular screening tests and scans.

What tumors are linked to MEN1?

There are three main types of tumor linked to MEN1. The tumors are usually *benign* (not cancer). These are found in:

1. The *parathyroid* glands in the neck;
2. The endocrine *pancreas* and gut (duodenum); and
3. The *pituitary* gland near the base of the brain behind the nose.

More than 8 out of 10 (80%) of MEN1 patients will have developed at least one of the tumors or have extra activity in a gland by the age of 40. This is around 4 out of 10 (40%) by the age of 20. Younger cases have been recorded. The condition varies greatly even within families, so that not everyone will have the same tumors and nor will they occur at the same age. Not all MEN1 patients will have all of the tumors detailed in this factsheet.

The first line of tests for most of the tumors linked to MEN1 is the checking of hormone levels using blood tests, as well as scans of the head, neck and tummy area. If a tumor is found, surgery may be needed to remove just the tumor or the whole of the affected gland.

Pancreatic neuroendocrine tumors in MEN1

In MEN1, about 3 in 4 people will develop a well-differentiated neuroendocrine tumor within the pancreas (pNET). The treatment of pancreatic tumors will depend upon the number, size and type of tumor(s), and the location in the pancreas.

Further information on pNETs can be found in our "What is Neuroendocrine Cancer of the Pancreas?" factsheet.

Parathyroid tumors

Almost all people with MEN1 will develop parathyroid tumors by the age of 40. The parathyroid glands lie just behind the thyroid gland in the neck, although sometimes in people with MEN1 there are extra glands in the upper chest. Rarely, they may be found inside the thyroid gland. The parathyroids are responsible for regulating the amount of calcium present in the body by releasing parathyroid hormone into the blood. This helps to keep the levels of calcium normal in the blood, bones and urine

By making too much parathyroid hormone, the tumors cause a condition called hyperparathyroidism. Symptoms include thirst, tiredness, aches and pains, memory problems, indigestion and depression. They can also eventually lead to osteoporosis or kidney stones.

Treating parathyroid tumors

Treatment involves removing the glands with tumors by surgery. These days, most surgeons will remove most of the parathyroid glands and just leave half of one gland (remnant) behind to help control the body's calcium levels (sub-total parathyroidectomy). If the remnant does not begin to work again, the patient will need lifelong medicine in the form of activated Vitamin D which helps the body to maintain a healthy level of calcium. Decisions regarding these issues will be discussed with you when you see your surgeon.

In MEN1, extra parathyroid glands may often be found in or around the thymus in the upper chest. Therefore, many surgeons also perform a thymectomy (removal of the thymus gland in the upper chest) at the same time as total parathyroidectomy. Removal of the thymus may also reduce the risk of developing a thymic neuroendocrine tumor

Pituitary tumors

Roughly 3 in 10 people with MEN1 will develop a tumor in the pituitary. The pituitary gland sits near the base of the brain behind the nose and under part of the eye nerves in a bony hollow called the sella turcica. Even though it is the size and shape of a bean, it is the master gland of the body's endocrine system. Pituitary hormones are important for growth and development, metabolism (turning food into energy) and reproduction. There are several different types of pituitary tumor that can occur in MEN1. None of them is cancerous. They can differ in size, with

those less than 10mm in diameter called microadenomas, and those of more than 10mm called macroadenomas. Macroadenomas can push on eye nerves and cause vision problems or stop the pituitary gland from working normally.

Types of pituitary tumors in MEN1

1. Prolactinomas – the most common pituitary tumor in MEN1, overproduction of the hormone prolactin can cause headaches, as well as lack of periods in women, and erectile dysfunction in men
2. Somatotrophinomas – can produce excess growth hormone causing acromegaly (gigantism)
3. ACTH-producing – produces too much of the hormone ACTH which affects the adrenal glands causing a condition known as Cushing's disease. Symptoms include weight gain, flushing on the face and neck, excess growth of body and facial hair, change of body shape and raised blood pressure
4. Non-functioning

Treating pituitary tumors

Treatment may be in the form of medicine or surgery. This will depend upon the type of tumor and its size. Sometimes small tumors can be treated with tablets or injections. In some cases (rarely) radiotherapy is needed if surgery alone does not control the growth.

Genetic testing explained

Chromosomes and genes

In each cell of the body there are 23 pairs of chromosomes that contain our genes. We inherit one chromosome from each pair from each parent. This means that we inherit one copy of each gene from each of our parents, thereby giving us two copies. In most people there are two normal functioning MEN1 genes. In patients with MEN1, one of this pair has a change (mutation). This can be inherited from either parent (inherited or familial) or can start in an individual for the first time (new mutation or de novo). When someone with MEN1 has children, they can pass on either the normal gene or the gene change. This is entirely random, like tossing a coin. Each child therefore has a 1 in 2 or 50% chance of inheriting the gene change, and is therefore at risk of developing the tumors in MEN1. This method of inheritance is called autosomal dominant inheritance.

Genetic testing

It is possible in some families to have a genetic test to see whether someone has inherited the gene change. The first step is to have a blood sample tested from someone with MEN1 in the family (mutation screen). A gene change is not always found. If a gene change is found, a blood test (predictive genetic testing) may then be offered to other members of the family. There are a number of issues surrounding predictive genetic testing particularly in relation to children and as such, all patients should be seen and counselled by a consultant clinical geneticist. If a gene change cannot be found or if a blood sample from an affected person cannot be obtained then predictive genetic testing cannot be done.

Having children tested is a very individual decision, however; if children of a parent with a known MEN1 gene change are tested and do not have that gene change they can rest assured that no further tests are needed. Those who have inherited the gene can be comforted by the fact that a screening plan will find and treat any tumors as early as possible. In this way, problems caused by ulcers and kidney stones as a result of parathyroid tumors, and advanced pancreatic islet cell cancer, may be drastically reduced.

Other tumors linked to MEN1

People with MEN1 may develop neuroendocrine tumors (NETs) in the chest or stomach area, as well as lipomas (benign tumors of fat cells), benign thyroid tumors and benign tumors of the outer layer of the adrenal gland (adreno-cortical adenomas).

Fewer than 1 in 20 people with MEN1 may have other neuroendocrine tumors (NET/NEN) in addition to the main tumors. These tumors make large amounts of the hormone serotonin, causing 'asthma', attacks of flushing and diarrhea (carcinoid syndrome). NETs are often found in the area of the lungs, thymus (top of the chest) or gut. Symptoms can be relieved in most patients using somatostatin analogues (SSAs). SSAs are given as regular injections of octreotide, lanreotide or pasiriotide to control tumor growth and hormone production. Surgery, radiotherapy or chemotherapy are also useful. The treatment for NETs of the middle gut is surgery or radionuclide therapy. Radionuclide therapy (PRRT) uses radioactive substances (Yttrium 90 or more commonly Lutetium 177) that are attached to octreotide and given by slow injection through a drip into the bloodstream. This may provide relief from symptoms as well as slow or stop further tumor growth. Usually 4 cycles are given, but sometimes an extra two may be given later. Other therapies aimed directly at the liver such as embolization or radiofrequency ablation may be used instead of or in addition to radionuclide therapy. NETs in the thymus gland at the top of the chest cause problems from local growth of the tumor rather than hormone production and are best treated with surgery. However, about 1 in 4 (25%) of thymic tumors produce ACTH and may cause Cushing's syndrome.

Other MEN1-like syndromes

In 1 in 4 (25%) of patients with a clinical diagnosis of MEN1, no gene change can be found. In these cases, re-testing for MEN1 every few years may find a newly discovered gene change. Otherwise, there are two other syndromes that are similar to MEN1, although much rarer, that can also be tested for:

MEN4 – in this syndrome, caused by a change in the *CDKN1B* gene, a person may develop parathyroid and pituitary tumors. It is thought that the tumors in MEN4 appear later in life than in MEN1.

Familial isolated pituitary adenomas (FIPA) – in this syndrome, usually caused by a change in the *AIP* gene, pituitary tumors are seen to run in families. These are often prolactinomas or growth hormone producing tumors and they may occur earlier in life than in MEN1.

Resources

Association for Multiple Endocrine Neoplasia Disorders

www.amend.org.uk

For the full list of INCA members: https://incalliance.org/members/