What Is Multiple Endocrine Neoplasia Type 2A (MEN2A)?

Multiple endocrine neoplasia type 2A (MEN2A) is a condition that can be passed down in families. MEN2A causes more than one gland of the body's endocrine (gland) system to develop tumors including neuroendocrine tumors (NETs). The affected glands may then produce 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 MEN2A.

Multiple = more than one

Endocrine = gland system

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

How is MEN2A diagnosed?

A person may be said to have MEN2A if they have:

1. 2 or more tumors that occur in MEN2A; or

2. only one tumor, but there is a family history of relatives with MEN2A; or

3. a blood test which shows a change in the RET gene

Someone may have the gene change that causes MEN2A, but not have developed any of the tumors. Due to the risk of developing the tumors in MEN2A, they should be offered a regular screening program.

What tumors occur in MEN2A?

There are three types of tumor that can occur in MEN2A. These are:

1. in the thyroid gland in the neck (medullary thyroid cancer)
2. in the parathyroid glands that lie close to or inside the thyroid (parathyroid tumors)
3. in the adrenal glands that sit on top of each kidney (pheochromocytomas).

The first treatment in MEN2A is usually for medullary thyroid cancer. This consists of surgery to remove the thyroid gland and surrounding lymph nodes. After this, management for the other tumors that occur in MEN2A involves checking hormone levels using blood and urine tests, and scans of the neck and stomach area. Sometimes this might lead to more treatment in the form of surgery to remove other tumors and/or affected glands.

Medullary thyroid cancer (MTC)

Almost all MEN2A patients will develop medullary thyroid cancer (MTC) by the age of 40. The thyroid gland is found at the front of the neck. MTC starts growing in the parafollicular

cells (C-cells) of the thyroid gland which make the hormone calcitonin. The state before the cancer develops is called C-cell hyperplasia, where there is abnormal growth of the normal C-cells and an increase in calcitonin production. MTC usually develops over a number of years from this abnormal growth but can spread early on to nearby lymph nodes, although there may be no physical symptoms. The risk of MTC varies according to the specific mutation in a family and this then influences discussions about the age at which surgery may be recommended in an affected child.

Treating MTC

If the thyroid and nearby lymph nodes are removed by surgery while the C-cell hyperplasia or cancer is still contained inside the thyroid (total thyroidectomy and central lymph node dissection), a patient is usually cured. If calcitonin levels are still above normal after surgery, this shows that the cancer has spread (metastatic) or has not been completely removed. In this case, more surgery and other treatments may be used to control it. As yet there is no complete cure for metastatic MTC; however, it may often be managed well and without symptoms for many years. Symptoms that may develop can sometimes be controlled by the use of radiotherapy and sometimes chemotherapy.

Due to the earlier detection of MEN2A, made possible by the genetic test, and the high chance that an MEN2A patient will develop MTC, surgery to remove the thyroid gland is now done in children who carry the gene. In some cases, the surgery is done before the age of 5 in order to prevent the development of the cancer. In older children, thyroidectomy is performed as soon as MEN2A is diagnosed.

More details on treating MTC can be found in our “What Is Medullary Thyroid Cancer?” factsheet.

Pheochromocytomas (‘fee-oh-cromo-sy-tomas’)

Pheochromocytomas (pheos – ‘fee-ohs’) are neuroendocrine tumors (NETs) of the adrenal glands. In MEN they are almost always benign (not cancer).

The body’s two adrenal glands are normally each about the size of a whole walnut and sit just on top of the kidneys. Pheos grow in the inner part of the gland (medulla) and make larger than normal amounts of a group of hormones called catecholamines (such as adrenaline). Pheos may grow for many years without causing severe symptoms, but they can start to do so due to events such as childbirth or surgery. Even though pheos are almost always benign in MEN, they are still a danger to the patient due to the sudden larger than normal amounts of hormones they make. They have been known to cause strokes, heart failure and premature death. Once a patient is known to have MEN2A, regular tests should find a pheo before severe symptoms develop.

Possible symptoms of a pheo may include all or some of the following: sudden headaches, palpitations, breathlessness, excessive sweating, high (or rarely low) blood pressure (either all the time or every so often), trembling, pale appearance, tiredness, depression, anxiety, and feeling sick with or without being sick.

How are pheos treated?

Treatment for pheos is usually surgery. The tumor and the adrenal gland where it grows are both removed. If only one gland has a tumor, then only that gland will be removed at that

time. This is because removing both glands will leave the patient needing corticosteroid drugs for the rest of their life to replace the hormones made by the glands. Doctors prefer to delay this type of drug treatment for as long as possible as the medication has its own potential drawbacks. Before surgery a drug (alpha-adrenoceptor blockade) is usually given to help make the blood pressure as stable as possible. This is needed because a pheo can cause sudden high blood pressure. Alpha-blockers (phenoxybenzamine or doxazosin) and sometimes beta-blockers (atenolol or propranolol) are often started outside of the hospital before surgery.

If both adrenal glands are removed, the two main drugs that a patient must take are hydrocortisone and fludrocortisone. They replace the hormones cortisol and aldosterone which are made by the glands. The drugs take over keeping blood sugar levels normal, aiding recovery from injury and stress, and keeping the balance of salts and water content of the body normal. Any adrenal surgery must be carried out by an expert, and some surgeons are able to perform 'cortex-sparing' surgery that means that the need for life-long hydrocortisone and fludrocortisone is lessened.

In some patients very small pheos may be found that do not make hormones, or that make low levels of catecholamines, and in certain cases, 'watch and wait' and medical treatment for blood pressure may be appropriate.

More information on tests and treatments for pheochromocytomas can be found in our "What Is Sporadic Pheochromocytoma/Paraganglioma?" factsheet.

Parathyroid tumors

Tumors in the parathyroid glands cause higher than normal levels of parathyroid hormone (PTH). They occur in fewer than 1 in 4 MEN2A patients. The parathyroid glands lie just behind the thyroid gland in the neck. 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.

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 MEN2A genes. In patients with MEN2A, 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 MEN2A 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 MEN2A. 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 MEN2A 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 MEN2A 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. Given the potential for affected children to develop MTC at a young age, many parents opt for testing their children in the first few years of life.

Other associated MEN2A conditions

Hirschprung's disease

Very rarely, some patients with MEN2A may also have a condition called Hirschprung's disease (HD). This would usually occur in early childhood and is most often seen in specific gene changes (codons 609, 618 and 620). Even so, not everyone with these gene changes will have HD. The reason why some people do and others do not is still not known.

HD is a bowel condition caused by a lack of nerve cells in part of the bowel. Symptoms can include tummy pain, bloating and constipation. Children may also not weigh as much as they should. In some cases, HD might sometimes cause vomiting or diarrhea. HD can be seen using an x-ray. Sometimes a small piece of tissue from the bowel is removed and looked at under a microscope. This is called a rectal biopsy and may require an anesthetic in older children.

HD can often be treated effectively by surgery in the hands of an experienced surgeon. Treatment may happen in stages over a period of several weeks or months. The section of bowel that is not working properly is removed and the two ends of the remaining healthy bowel would be joined together.

Lichen amyloidosis

Cases of a skin condition called familial lichen amyloidosis have been seen in some families with MEN2A, but this is very rare. This appears as itchy, raised, rash-like areas of skin that are slightly darker than the surrounding skin. These patches usually occur on the upper back in MEN2A and may be caused by repeated scratching (see itchy back below).

Itchy back (pruritis)

Many patients with MEN2A (codon 634) have a very itchy upper back. This often starts in childhood for reasons which are not yet understood. Repeated scratching in this area is thought to cause lichen amyloidosis (see above).

Resources

Association for Multiple Endocrine Neoplasia Disorders

www.amend.org.uk

Pheo Para Alliance

www.pheopara.org

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