What Is Multiple Endocrine Neoplasia Type 2B (MEN2B or MEN3)?

Multiple endocrine neoplasia Type 2B (MEN2B) is a condition that can be passed down in families. MEN2B 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 MEN2B. MEN2B is also sometimes known as MEN3.

Multiple = more than one

Endocrine = gland system

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

How is MEN2B diagnosed?

A person may be said to have MEN2B if they have:

1. 2 or more tumors that occur in MEN2B; or

2. only one tumor, but there is a family history of relatives with MEN2B; or

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

As well as endocrinologists, doctors in a range of other areas of medicine might suspect MEN2B. Pediatricians (children's' doctors) may suspect MEN2B when a young child or baby has growth or eating problems affecting development (failure to thrive), or if the child does not produce tears while crying. A dentist or doctor may suspect MEN2B when they see lumps (mucosal neuromas) in the mouth (gums and/or tongue) or the lumpy lips which are a typical facial feature of MEN2B. Bowel doctors (gastroenterologists) may also suspect MEN2B if the cause of enlarged bowel (megacolon), constipation and/or diarrhea is found to be the result of benign colon growths called ganglioneuromas.

What tumors occur in MEN2B?

There are three types of tumor that can occur in MEN2B. 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)

In addition, patients with MEN2B often have benign (not cancer) lumps on the lips, in the mouth and throughout the gut. Children with MEN2B are more likely to have feeding problems and bowel problems than other children.

Medullary thyroid cancer (MTC)

Almost all MEN2B patients will develop medullary thyroid cancer (MTC), sometimes within the first year of life, unless steps are taken to prevent it. 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. In MEN2B, MTC develops at a very early age and can quickly spread to nearby lymph nodes. Even so, there may be no physical symptoms of this. As MTC grows, calcitonin levels increase.

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 using radiotherapy and sometimes chemotherapy.

Due to the earlier detection of MEN2B made possible by a genetic test, and the high chance that an MEN2B patient will develop MTC in early childhood, surgery to remove the thyroid is done in the child's first year in order to prevent the development of the cancer. In older children, thyroidectomy is performed as soon as MEN2B is diagnosed.

More details on treating MTC itself 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 MEN2B 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 MEN2B, 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 MEN2B, 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.

Other associated MEN2B conditions

Ganglioneuromas

Ganglioneuromas are benign tumors (not cancer) of areas of nerve tissue in the gut. They occur in almost all MEN2B patients and can grow anywhere from the mouth down to the rectum.

These tumors often cause no symptoms, but those along the gut may cause a swollen belly, and a change in shape of the bowel (megacolon) that can cause diarrhea or constipation. These problems may be seen in early childhood in some MEN2B patients and may sometimes require surgery.

Ganglioneuromas in and around the mouth (mucosal neuromas) are the cause of the swollen lips and lumps on the tongue and/or gums often seen in MEN2B patients. Some growths can be removed, especially if they cause problems with brushing teeth. A similar tumor (neuroma) can also occur along the eyelids of patients with MEN2B.

Marfanoid habitus

MEN2B patients are often tall and thin with long fingers and toes. This is due to common abnormalities affecting muscles and/or bones (marfanoid habitus). Orthopedic issues like

these can also include foot and hip abnormalities, hypermobile joints, and scoliosis. People with MEN2B do not have Marfan syndrome.

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 MEN2B genes. In patients with MEN2B, 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 MEN2B 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 MEN2B. This method of inheritance is called autosomal dominant inheritance.

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In most people there are two normal functioning MEN2B genes (RET or RET proto-oncogene). In patients with MEN2B one of this pair has a change (sometimes called a ‘mutation’). The most common gene change in MEN2B is called ‘M918T’.

The gene change can be passed down to a child from either parent, but in most people with MEN2B, it started in that person for the very first time (new or de novo mutation). However, once someone with MEN2B has children they can pass on either the normal gene or the gene with the change. This is random like tossing a coin. Each child of an affected parent thus has a 1 in 2 or 50% chance of inheriting the faulty RET gene. This child would then be at risk of developing the tumors of MEN2B. It also means that there is a 50% chance that the child would inherit a normal copy of the gene and would therefore not inherit MEN2B. This method of inheritance is called autosomal dominant inheritance.

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/