Patient Information Leaflet

Multiple Endocrine Neoplasia
Type 2a
(MEN2a)

MEN 2 LINK NUMBER

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What is Multiple Endocrine Neoplasia Type 2a?

*Multiple Endocrine Neoplasia Type 2a (MEN2a)*, also known as Sipple’s Syndrome, is one type of a group of genetic disorders under the name Multiple Endocrine Neoplasia, the other types being called MEN1, MEN2b and FMTC (*see separate leaflets*). They are inherited disorders, which cause more than one gland of the body’s endocrine (gland) system to develop tumours. The affected glands then produce abnormally increased amounts of hormones, the body’s chemical messengers, which in turn cause a variety of different symptoms. Each type of tumour may occur alone and independently of MEN.

The associations between the different conditions within MEN2a were first described in 1961 by Dr Sipple and thus referred to as Sipple’s Syndrome. In 1962 Sipple’s Syndrome was confirmed to be an hereditary condition. In 1993, the gene responsible for MEN2a, the RET proto-oncogene, was identified by Professor Bruce Ponder from Cambridge in the UK.

How is MEN2a Diagnosed?

A diagnosis of MEN2a may be arrived at if the patient falls into one of three different categories:

1. ***MEN2a by definition;*** when 2 or more MEN2-associated tumours are present (*see What Conditions are Associated with MEN2a*);
2. Familial MEN2a; where the patient may only have one tumour, but there exists a family history of relatives with more than one MEN2-associated tumour;
3. MEN2a carrier; where a patient is recognised as carrying the genetic mutation responsible for MEN2a, even if there are no tumours present in that patient at that time. A MEN2a carrier is identified by positive DNA test (*see Genetic Testing Explained*). This test is usually performed for children of known affected families or if a patient has more than one associated tumour and who may therefore be the first identified of a new affected family. The discovery of the MEN2 gene has helped to identify individuals at risk of inheriting MEN2a, and to reassure other family members who are not at risk.
What Conditions are Associated with MEN2a?

There are three types of tumour associated with MEN2a. These occur in the thyroid in the neck (medullary thyroid cancer), the parathyroid glands that lie close to or within the thyroid (parathyroid tumours), and the adrenal glands that sit atop the kidneys (phaeochromocytomas). The remainder of this information leaflet is divided up between these conditions and details the current thinking on appropriate tests, treatment and medications.

Initial treatment for most of the conditions associated with MEN2a is the monitoring of hormone levels using blood and urine tests, scans of the neck and abdominal area, sometimes leading to the surgical removal of the tumour and/or affected gland.

Table 1 below details the current medical strategies for testing MEN2a patients according to their particular codon mutation. See specific condition sections for more details on the tests themselves.

**Table 1. (Recommended testing programme for MEN2a patients)**

<table>
<thead>
<tr>
<th>DISEASE AND CODON MUTATION</th>
<th>CLINICAL TESTING ACCORDING TO SPECIFIC RET GENE MUTATION WITHIN THE FAMILY</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medullary Thyroid Cancer (MTC)</td>
<td>Plasma calcitonin (CT) levels</td>
<td>Annual + pre/post total thyroidectomy</td>
</tr>
<tr>
<td>Phaeochromocytoma</td>
<td>Catecholamines and metanephrines in 24hr urine collections</td>
<td>Annual, from age 5</td>
</tr>
<tr>
<td>Codons: 634, 918</td>
<td>Catecholamines and metanephrines in 24hr urine collections</td>
<td>2-yearly, from age 10</td>
</tr>
<tr>
<td>Codons: 609, 768, 804, 891</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Plasma calcium and parathyroid hormone levels</td>
<td>Annual</td>
</tr>
<tr>
<td>Codons: 634</td>
<td>Plasma calcium and parathyroid hormone levels</td>
<td>2-yearly, from age 10</td>
</tr>
<tr>
<td>Codons: 609, 611, 618,620, 790, 791</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codons: 768, 804, 891</td>
<td>Only if showing symptoms (rare)</td>
<td>Only if showing symptoms</td>
</tr>
</tbody>
</table>

**MEN2b & FMTC**: MEN2a is closely related to though different from 2 other MEN syndromes, MEN2b and FMTC. FMTC consists of the hereditary form of MTC without any other glands being involved. MEN2b patients may have MTC (almost all patients), phaeochromocytomas (50% patients) and rarely parathyroid tumours. In addition, patients with MEN2b may have long fingers and toes and an unusual distinctive facial appearance.
Almost 100% of MEN2a patients will develop medullary thyroid cancer (MTC) by age 40. Its level of aggressiveness is determined by which RET codon is mutated. The thyroid is situated at the front of the neck. This gland produces 3 hormones: thyroxine and triiodothyronine, which are essential for maintaining the body’s metabolism and mental and physical development, and calcitonin, which lowers blood calcium levels.

MTC occurs in the calcitonin-producing cells (parafollicular or C-cells) of the inner part of the thyroid, called the medulla. The precursor to MTC is called C-Cell hyperplasia, where there is abnormal growth of the normal C-cells and overproduction of calcitonin. MTC usually develops over a number of years from this abnormal growth but can spread early on to nearby lymph nodes. If the thyroid and nearby lymph nodes are surgically removed while the C-cell hyperplasia or cancer is still contained within the thyroid (total thyroidectomy and central lymph node dissection), a patient is usually cured. If, after surgery, calcitonin levels are still raised, this indicates that the cancer has spread (metastatic), and so further surgery and therapies are used to control it. As yet there is no definitive cure for metastatic MTC, as it rarely responds to regular chemotherapy or radiation treatments. Nevertheless, it is usually slow growing and may often be managed effectively and without symptoms for many years.

Due to the earlier detection of MEN2a made possible by the genetic test, and the high probability that an affected patient will develop MTC, thyroidectomy is now performed in affected children before the age 5. This course of action may be responsible for drastically reducing the number of deaths in MEN2a patients from metastatic MTC from 15-20% to just 5%.

THE LYMPHATIC SYSTEM
The Lymphatic system is a network of vessels that transport lymph from the tissue fluids into the bloodstream. Lymph is the fluid that bathes the tissues, which is derived from the blood and is drained by the lymphatic vessels. Lymph passes through a series of filters called lymph nodes and is ultimately returned to the bloodstream. Due to this transportation-like system, local lymph nodes (the filters) are often removed during cancer surgery to minimise the risk of the cancer spreading to other sites in the body.

“My son had his thyroidectomy at age 3. We were so terrified but everyone at the hospital was great. He was sitting up tucking into a jam sandwich within an hour of waking up from the anaesthetic and running around in the playroom in under 2 hours – he put us adults to shame!”

Thyroid
**Baseline Calcitonin:** This blood test measures the levels of the hormone calcitonin in the blood. Elevated levels of calcitonin could indicate the presence of c-cell hyperplasia or MTC. The blood must be taken immediately and on ice to a chilled centrifuge in the lab.

**Pentagastrin Stimulation:** Another test for measuring calcitonin levels and thereby presence of C-cell hyperplasia or MTC. This is a longer and more complicated blood test than the baseline calcitonin, requiring the patient to fast beforehand. A substance called Pentagastrin is injected first and causes momentary side effects in the patient, including flushing, nausea, and a feeling of needing to use the toilet. The blood samples are then taken at timed intervals of 1, 2, 3, 5 and 10 minutes and, once again, must be taken immediately to the lab on ice.

**TOTAL THYROIDECTOMY:** A small incision is made at the base of the front of the neck from which the thyroid and nearby lymph nodes can be removed.

**Hospitalisation:** approx 3-5 days. Eating and drinking is possible almost immediately, although feels rather strange.

**Risks:** damage to vocal chords; unavoidable removal of or damage to the parathyroid glands resulting in a drop in calcium levels in the blood. Symptoms of parathyroid damage include tingling lips, fingers and toes, and eventually cramping. If they cease to function altogether or are removed, the patient will require additional lifelong medication (see Treating Parathyroid Tumours).

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**Table 2. (Recommended age for Thyroidectomy in MEN2 patients)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mutated Codon in the RET Gene</th>
<th>Age of Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>883, 918, 922</td>
<td>Early in the 1st year</td>
</tr>
<tr>
<td>2</td>
<td>611, 618, 620, 634, 891</td>
<td>Before 6 years of age</td>
</tr>
<tr>
<td>3</td>
<td>609, 760, 790, 791, 804</td>
<td>After abnormal results on C-cell stimulation testing</td>
</tr>
</tbody>
</table>

“Supper was served not long after returning to the ward after my thyroidectomy. I was extremely wary about eating as my throat felt so strange, however after mixing mash potatoes with soup for my main course and finding no problems eating that, I finished off with a hard and juicy apple for dessert!”
**Treating MTC (continued)**

**THYROIDINE:** a very effective artificial replacement for the thyroid hormones that must be taken life-long after thyroidectomy. Tablets are taken once a day and doses vary between 100-150mcg. Regular blood tests are required to ensure the right dose is being prescribed.

**Treating Metastatic MTC**

If, after surgery, calcitonin levels are still raised, this may indicate that the cancer has spread (become metastatic), and so further surgery and therapies are used to control it. Sometimes a patient may still be cured by meticulous removal by surgery of further lymph nodes, particularly under the arms and around the chest area.

**MIBG THERAPY:** Where surgery is no longer an option due to the extent of the disease, some specialised medical centres may use $^{131}$I-meta-iodobenzylguanidine ($^{131}$I-mIBG), a radioactive therapy with few side effects, to help reduce or control the spread.

[Professor Ashley Grossman/Dr Karim Meeran, please expand........]
Phaeochromoctyomas (phaeos) are benign tumours of the adrenal glands. The body's two adrenal glands are normally about the size of a whole walnut, and sit just on top of the kidneys. Phaeos occur in the inner part of the adrenal gland (the medulla) and produce excess amounts of a group of hormones called catecholamines (including adrenaline). They may grow for many years without severe symptoms, but can be activated by events such as childbirth.

Although when occurring in MEN patients they are benign, these tumours are accountable for the majority of early and sudden deaths from stroke and heart failure in undiagnosed MEN2 patients due to the sudden quantities of hormones produced. Unless a patient is already known to have MEN2a, phaeos are notoriously hard to diagnose as the symptoms may be very varied.

Symptoms may include all or some of the following: migraine-like headaches, palpitations, breathlessness, excessive sweating, high (or rarely low) blood pressure (sustained or episodic), trembling, pale appearance, lethargy, depression and anxiety. As well as variety, the symptoms may not be constant, often coming and going in “attacks” (termed: episodic).

[Good annotated adrenal gland diagram w/wo phaeo needed!]
Testing for Phaeochromocytomas

24 HOUR URINE CATECHOLAMINES: A collection of a patient’s urine over 24 hours to measure quantities of catecholamines in the body. Raised levels would suggest the presence of a phaeo. Collection bottles should not contain any acid and should not be refrigerated during the 24 hours of the test.

24 HOUR URINE METANEPHRINES: [Professor Ashley Grossman/Dr Karim Meeran – please explain - if indeed it is still used]

MAGNETIC RESONANCE IMAGING (MRI) SCAN: You will be asked to lie still in a confined tube-like machine for up to 1 hour, periodically being required to hold your breath and often part-way through being given an injection of contrast to highlight specific areas of interest within the body.

MIBG SCAN: This radioactive scan is usually only performed in specialist nuclear medicine departments in the larger or university hospitals. The process takes two days, although the scan itself will only take about 1 hour on each day. Before the scan the hospital will supply you with potassium iodate tablets, which you must take prior to the scan to protect your thyroid gland (even if you no longer have one!).

Day 1: you will be asked to lie still under a large camera-like scanner and general pictures will be taken. You will then be given an injection of radioactive material to highlight areas of activity in your abdomen. Marks may then be placed on your abdomen and further scans done.

Day 2: Lining the machine up using the marks on your body, a further scan will be done to record which areas are still absorbing the radioactive material.

Once a phaeochromocytoma is diagnosed, treatment with alpha-blockade and beta-blockade (see Treating Phaeochromocytomas) is started in order to control the rise in blood pressure and thereby prevent strokes, heart attacks and death.
Treating Phaeochromocytomas

Treatment for phaeochromocytomas is the surgical removal of the affected adrenal gland. If only one gland is affected then only that gland will be removed at that time. This is because, removal of both adrenal glands means that the patient will be reliant on lifelong replacement corticosteroid drugs. The preference is to delay this type of drug treatment for as long as possible owing to the medication’s own potential drawbacks (see Bilateral Adrenalectomy).

**Right Hand (RH) Adrenalectomy**: removal of the right side adrenal gland only  
**Left Hand (LH) Adrenalectomy**: removal of the left side adrenal gland only  
**Bilateral Adrenalectomy**: removal of both adrenal glands at the same time.

Considerable pre-surgical preparation called **Alpha-blockade** is required in all cases as a functioning phaeo makes the patient's blood pressure extremely unstable. Blood pressure is stabilised using blood pressure medications called **Alpha- and Beta-blockers** (eg. phenoxybenzamine and atenolol respectively). Since this pre-op oral medication regime was introduced, deaths caused by the affects of a phaeo during surgery have dropped from 40% to only 3-5%. In order to minimise all risks, this preparation is also undertaken in cases of non-functioning phaeos.

Alpha-blockade is usually done as an in-patient so that the drugs’ affects on your blood pressure can be closely monitored. Initially, only the alpha-blocker is started and this has several side-affects, including dizziness, dry mouth and stuffy nose. A positive side affect is that this medication will stop the hypertension “attacks” caused by the phaeo. The overall aim is to induce orthostatic hypotension in the patient, where the blood pressure falls on standing. When this is achieved the beta-blockers are added and the patient may rest at home for several days or weeks prior to surgery. The symptoms lessen during this time, although the patient will still feel very tired and become easily breathless and dizzy.

**Surgery**: Surgical technique depends upon the experience of the surgeon and the size of the tumour. Tumours of less than 5cm may be removed laparoscopically (ie through a series of small incisions in the abdomen). Larger tumours may be removed either through a larger incision in the abdomen or through the back by removing the lower rib.

**Hospitalisation**: pre-surgery for alpha-blockade, approx 7-10 days; post-surgery approx 1 - 2 weeks depending upon surgical method and whether single or bilateral surgery.

**Risks**: sudden surges in blood pressure from surgeon's handling of the tumour during its removal, causing stroke and heart failure, however these risks have been drastically reduced since the introduction of Alpha-blockade.
BILATERAL ADRENALECTOMY: If both adrenal glands are removed, the patient will have to take life-long replacement medication in the form of steroids (corticosteroids). A patient will effectively have Addison’s Disease (though only the resulting condition rather than the disease itself), and the Addison’s Disease Self Help Group (ADSHG, see Useful Organisations) is a fantastic source of information on managing life on steroids.

The two main drugs that a patient must take after bilateral adrenalectomy are hydrocortisone and fludrocortisone. They replace the cortisol produced by the adrenal glands. The drugs take over in the maintenance of normal blood sugar levels, the promotion of recovery from injury and stress, and the regulation of the balance of mineral salts and water content of the body.

Interestingly, the well-known hormone, adrenaline does not need to be replaced in drug form because it’s close relative, nor-adrenaline, which has much the same function, is produced by the nerve endings throughout the body.

Hydrocortisone: Brand names Hydrocortone, Efcortesol. Tablet usually taken in split dose (eg. 10mg + 5mg +5mg) early morning, lunchtime and in the evening. At times of extra stress, i.e. surgery, injury, severe vomiting and diarrhoea, extra hydrocortisone is required immediately to eliminate the risk of irreversible hypovolaemic shock leading to loss of blood pressure and ultimately death. For this reason, all bilateral adrenalectomy patients should be issued with an emergency hydrocortisone injection kit before they leave hospital to keep at home and/or in the car. (Further information is available from ADSHG – see Useful Organisations).

Fludrocortisone: Brand name Fludrocortone. Regulates the balance of mineral salts and water in the body. Tablet taken x1 daily early morning.

Lansoprazole: Taken to offset the possibility of long-term steroid replacement causing stomach ulcers. Capsule taken x1 daily (15-30mg)
Parathyroid Tumours

Parathyroid tumours causing Hyperparathyroidism occur in less than 25% of MEN2a patients. The parathyroid glands lie just next to or are sometimes contained within the thyroid in the neck and as such are often unavoidably removed during total thyroidectomy for medullary thyroid cancer. Parathyroids are responsible for regulating the amount of calcium present in the body by releasing parathyroid hormone into the bloodstream, which helps to maintain the normal supply of calcium in the blood, bones and urine.

When tumours develop within the parathyroid glands the body is fooled into releasing calcium from the bones into the bloodstream and if left undetected can cause **osteoporosis** (brittle bones). You may at some point be given a bone density scan which is easy and takes little time. Another problem associated with parathyroid tumours is too much calcium in the urine, which may lead to kidney stones. In fact, the symptoms of parathyroid tumours have become known in the medical profession as “moans, groans, stones and bones”. Patients can suffer from poor memory, irritability, ulcers, kidney stones, pancreatitis and bone fractures, as well as the osteoporosis already mentioned. Other symptoms may include tiredness, muscle or bone pain, indigestion and constipation.

"After an operation to remove all four of my parathyroids, I took a month or two to get my calcium, Vitamin D and magnesium supplements in balance. Once this was achieved I felt as if a weight had been lifted from my shoulders, and according to the rest of the family, I was much less irritable!"

Testing for Parathyroid Tumours

**Blood calcium levels (serum calcium):** A relatively simple blood test for the patient.

**Parathyroid hormone (PTH):** Straightforward blood test.

**Sesta-MIBI scan of neck area:** This scan may be performed, not to diagnose affected parathyroids, but to locate them for surgery. A sesta-MIBI scan takes around 2 hours to perform. The radioactive sesta-MIBI is injected into the patient where it is taken up by the affected gland(s). Pictures are taken of the area immediately after the injection, and then 1 hour 45 minutes to 2 hours afterwards. The affected glands are those that are still lit up at the end of the scan.
Treatment is by surgical removal of the affected gland(s). In MEN, controversy remains as to whether to remove all four parathyroid glands even if they are not all affected. Some surgeons advocate total parathyroidectomy (removal of all 4 at once) because it is more or less certain that if one is affected, all will eventually be affected and that this will save future surgery in the same area. Other surgeons maintain that affected glands should be removed individually as and when a tumour arises (partial parathyroidectomy). Another controversial issue revolves around the decision whether or not to perform a parathyroid transplant (usually into the arm).

In the event of total parathyroidectomy, either alone or as part of a total thyroidectomy, the patient will require lifelong replacement medication with a form of Vitamin D (see below).

**Surgery:** The surgeon makes a 4-5cm incision at the base of the throat.

**Hospital stay:** approx 1 week. It is possible for the patient to be up and about, eating and drinking the same or next day.

**Risks:** Potential but rare voice box or nerve damage. Following surgery, patients may have episodes of low calcium (hypocalcaemia) causing tingling fingers, toes and lips and sometimes cramping, and will therefore need replacement medication

**Alfacalcidol,** (brand names, AlfaD, ergocalciferol): Vitamin D supplement in capsule form to help absorb calcium from the patient’s diet. This is frequently the only life-long medication required after parathyroidectomy.

**Calcium Carbonate,** (brand name, Calcichew): chalk-like tablet to be chewed/sucked to combat more severe cases of low calcium in the blood/body (hypocalcaemia). This is often used as a temporary calcium “top-up” after surgery, but not necessarily required life-long. Too large a dose or an indication that this supplement is no longer needed may become apparent if the patient begins to suffer from severe headaches, nausea and vomiting.

**Magnesium supplement,** this may be in the form of an injection or a tablet (e.g. magnesium glycerol-phosphate).

**Research:** A new class of drugs called calcium sensing receptor agonists (calcimimetics) is currently under investigation. In the future, these may be used to act directly on the parathyroid and perhaps even decrease parathyroid growth.
MEN2a is caused by a mutation (change) in the RET proto-oncogene. Genes are the unique set of biological information, which make each of us an individual. Every single building block, or cell, of your body contains this information, which we inherit from our parents. The genes are contained in 23 pairs of chromosomes within the nucleus (core) of each and every cell. Chromosomes may be referred to as the filing cabinets of the body containing files in the form of genes that, in turn, contain all the information your body needs to work properly … or not! Information in genes is written in a chemical “code” consisting of four chemical substances, abbreviated to the four letters: A, T, C and G which are repeated over and over in different combinations to give different instructions. This “code” is also called DNA (deoxyribonucleic acid).

For the patient, the DNA or genetic test is a simple blood test. The test looks at the order in which the chemical “letters” of the genetic code are placed within a gene. Mutations occur when there is a mistake in this code. If the test is done in a family where others have already tested positive for MEN, it is like looking in just a single book for a spelling mistake because there is already a result with which to compare it. If the test is the first done in an unknown family it is more like the laboratory is looking through an entire library for a single spelling mistake! Hence a possible time difference in obtaining results of between 6 weeks to 6 months.

In the MEN2 gene, the mutation can occur in one of several different areas called codons. Research has determined that mutations of different codons can relatively accurately predict to what extent and at what age the MEN2 conditions will manifest themselves. Ultimately, this knowledge enables doctors to tailor testing and treatment programmes to the patient’s needs accordingly.

Some families may exhibit several MEN-attributable conditions and yet have a negative genetic test. It is suggested that these people be kept under review.

MEN is an autosomal dominantly inherited disorder. In short, this means that your children would have a 1 in 2 or 50% chance of inheriting the mutated gene. Unless you are the first (spontaneous) MEN gene mutation in your family, there is also a 50% chance that one of your parents has or had the disorder.
Having children tested is a very individual decision, however, if children of a known MEN2a parent are tested, those unaffected can rest assured that no further investigations are required. Those who have inherited the gene can be comforted by the fact that testing and treatment patterns will determine as early as possible when intervention is required. Thanks to this early detection by DNA test, complications from advanced medullary thyroid cancer, and high blood pressure, stroke and heart failure due to adrenal tumours, and kidney stones as a result of parathyroid tumours, may be drastically reduced.

The UK Society for Endocrinology states that “the majority of physicians feel that genetic testing would be of enormous benefit in helping guide management and care of patients”.

Genetic testing and counselling is available at 20 regional genetic centres throughout the UK (see our leaflet on Genetics). A referral to a genetic centre is usually made through your GP or specialist.
Useful Organisations

The British Thyroid Foundation
PO Box 97
Clifford
Wetherby
West Yorkshire
LS23 6XD
Tel: 0870 770 7933
www.btf-thyroid.org.uk

ADDISON’S DISEASE SELF HELP GROUP
(ADSHG)
21 George Road
Guildford, Surrey
GU1 4NP
Tel/Fax: 01483 830673
www.adshg.org.uk

Genetic Interest Group (GIG)
Unit 4D, Leroy House
436 Essex Road
London
N1 3QP
Tel: 020 7704 3141
www.gig.org.uk

Contact a Family
209-211 City Road
London
EC1V 1JN
Tel: 010 7608 8700
www.cafamily.org.uk
About AMEND

AMEND was set up in 2002 by Liz Dent and her daughter Emily Sole who both have MEN1. They were concerned that, being diagnosed with a rare condition, there was little information to be found regarding best treatment, and even fewer fellow patients with whom to be in contact to share experiences - a process that so many people find helpful.

We hope that this information will go some way to making your choices easier to understand and therefore possibly easier to make.

The aims of AMEND are to improve the well-being of all persons affected by MEN by providing them with information in the form of leaflets and medical journal extracts, and promoting a wider knowledge of MEN among the medical profession to assist in early and accurate diagnosis.

In addition, AMEND have a number of trained Telephone Buddies who are patients and carers affected by MEN themselves. Should you wish to contact them, having someone else in a similar situation to yourself to talk to may make things easier to cope with.

Membership is just £15 per annum (£10 per annum unwaged/student/OAP). Just call the number on the front cover to ask for a membership pack. Members receive a quarterly newsletter containing interesting and relevant news and other articles, as well as an “Ask the Doctor” section, invitation to AMEND’s annual assembly, automatic updates on any recent medical and surgical advances and the opportunity to become a Telephone Buddy.