Phaeochromocytomas & Paragangliomas (incl MEN and SDHx)

Patient Information

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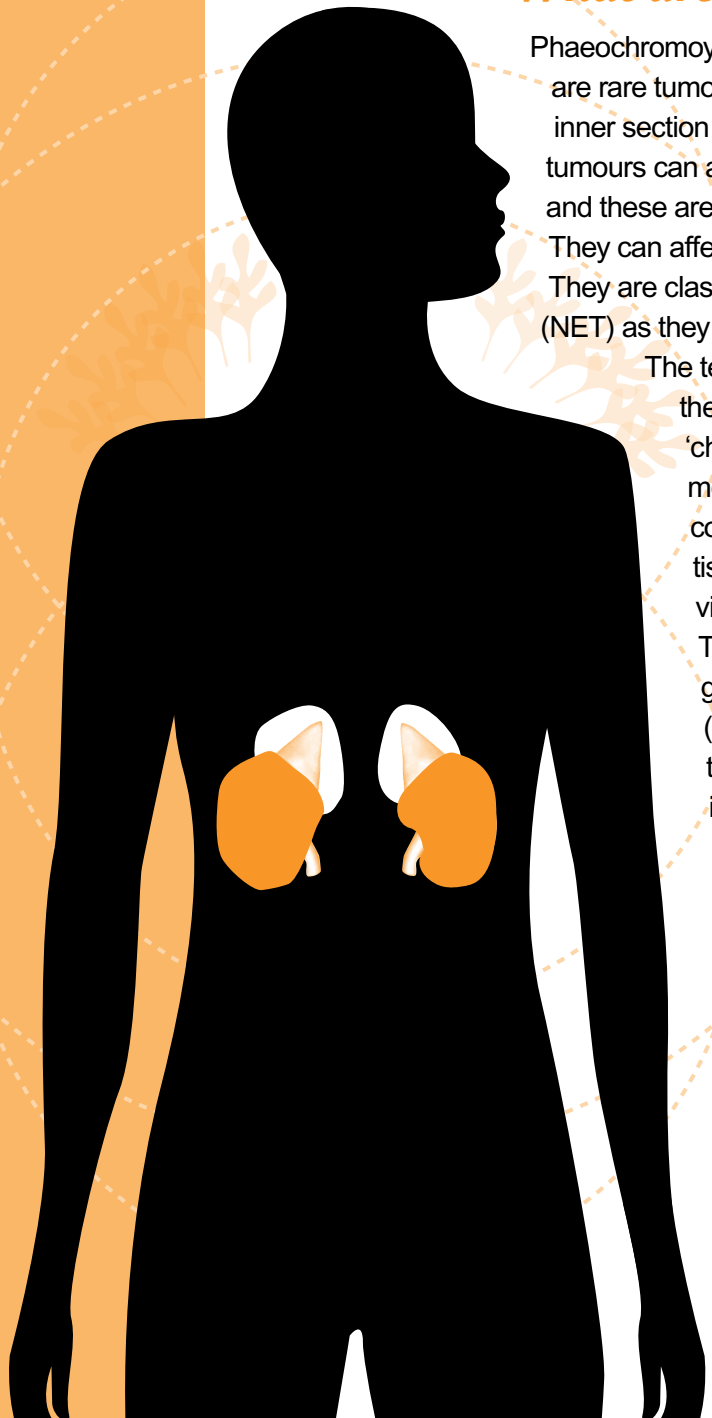


What are Phaeochromoytomas?

Phaeochromoytomas, often known as 'phaeos' ('fee-ohs'), are rare tumours of the adrenal gland arising from the inner section of the gland called the medulla. Similar tumours can arise from sites other than the adrenal gland and these are called extra-adrenal paragangliomas. They can affect people of all ages, including children. They are classified as a type of neuroendocrine tumour (NET) as they secrete certain peptides and hormones.

The term phaeochromocytoma is derived from the greek words 'phious' meaning dusky, 'chromo' meaning colour and 'cytoma' meaning tumour. It refers to the brownish colour the tumour cells develop when the tissue is treated with special chemicals to view them under a microscope.

The body has two walnut-sized adrenal glands, one above each of the kidneys ('adrenal' means next to the kidney). Even though the glands are small they are important as they produce several essential hormones. The medulla (the area of the adrenal gland from which phaeos arise) produces a number of hormones called catecholamines, mainly adrenaline and noradrenaline. These hormones help the body deal with maintaining blood pressure, deal with sudden stress or threats. Phaeos may produce excessive amounts of these hormones, causing a variety of symptoms that can affect the whole body.

What is known about these tumours?

- This type of tumour is rare occurring in 1 per 100 000 people per year.
- The majority (approximately 90% or 9 out of 10) are benign tumours (i.e. not cancer).
- Over 80% (8 in 10 cases) arise in the adrenal glands
- The most common age for diagnosis is between the ages of 30-60 years of age, although 10% arise in children.
- There is no sex difference or racial disposition.
- Tumours occurring in children are more likely to be related to an inherited condition than those occurring in adults.

Is there a genetic link?

- The majority of these tumours are not linked to a genetic condition and are therefore known as 'sporadic' tumours.
- Approximately 25% (1 in 4 cases) are related to inheriting a gene change which leads to an increased risk of developing phaeochromocytoma.
- The inherited forms can occur in syndromes, including: multiple endocrine neoplasia 2 (MEN-2), neurofibromatosis, von-Hippel Lindau syndrome and familial paraganglioma syndrome.
- There are families who develop phaeos with paragangliomas due to a very rare change in the succinate dehydrogenase (SDH) gene (see 'Inherited Paraganglioma Syndromes').
- Multiple Endocrine Neoplasia type 2 (MEN2): approximately 50% (1 in 2) of patients with a gene change that causes MEN2 will develop phaeos, often in both adrenal glands though not necessarily at the same time. They are almost always benign (not cancer) in MEN and would be treated in the same way as a sporadic phaeo. In addition to phaeos, patients with a MEN2 gene change almost always develop a rare form of thyroid cancer (medullary thyroid cancer) and less commonly, benign tumours of the parathyroid glands in the neck which may cause raised levels of calcium in the blood.

What are the symptoms of phaeochromocytomas?

Phaeos can cause a wide variety of symptoms which are mainly related to the release by the tumour of excessive amounts of hormone, mainly adrenaline and noradrenaline. Symptoms can occur intermittently often in episodes lasting only 15 minutes and may include some or all of the following:

- Headaches
- Dizziness
- Facial paleness (pallor)
- Excessive sweating
- Racing heart rate (palpitations)
- Panic attacks/ sense of doom
- Anxiety
- Weight loss
- Heat intolerance
- High (and rarely low) blood pressure (sustained or episodic)
- Nausea (with or without vomiting)
- Breathlessness
- Depression
- Lethargy

Many of the symptoms listed above are related to the high blood pressure (hypertension) that can be caused due to this condition. It is thought one case of hypertension in every 1000-2000 patients is due to phaeochromocytoma. Hypertension in patients with undiagnosed phaeos can be very difficult to control; however, once a diagnosis is made, special drugs are available to help to control it.

Phaeos in children

In children most phaeos occur in just one adrenal gland, however, in 20% (1 in 5) of cases they can affect both glands.
Approximately 1 in 3 young patients have tumours outside the adrenal gland with or without a tumour inside the gland.
The initial symptoms in children are similar to those of adults, including headache, fast heart rate and sweating. Their blood pressure is often raised. Children require the same investigations as adults to determine the underlying cause and make a diagnosis.

How are phaeos diagnosed?

Unless a patient is known to have a higher risk of developing tumours due to an inherited condition such as MEN2, phaeos are notoriously hard to diagnose as the symptoms may be very varied and often occur in episodes or sudden attacks lasting less than 15 minutes. If a phaeo is suspected a number of various tests may be recommended by your doctor. These may include:

24 hour urine test (catecholamines):

This test measures the amount of catecholamines that are excreted in the urine over a 24 hour period. In phaeos this level will be much higher than normal. The collection bottles contain acid as a preservative and should not be refrigerated. This test in good in helping diagnose phaeos but is not 100% accurate and so multiple collections may be required as well as other tests listed over.

24- hour urine test (metanephrines): This test is similar to the previous one but measures the level of metanephrines in the urine excreted over 24 hours. Metanephrines are breakdown products of adrenaline and noradrenaline. The urine collection bottles do not contain acid and should not be refrigerated.

Plasma Metanephrine Test:

Increasingly, plasma (blood) metanephrine and normetanephrine tests are being used to identify the presence of a phaeo. This test should be performed after the patient has been lying quietly for about 30 minutes to avoid a false positive result.

CT scan: a computer tomography scan provides a three dimensional picture of the inside of the body. It can be used to determine the position and size of tumours.

MRI scan: this magnetic resonance imaging (MRI) scan can help reveal where the tumours are positioned. It uses magnetism rather than x-rays to take pictures of the inside of the body.

MIBG scan: a specialised scan performed at the hospitals nuclear medicine department. MIBG (Meta iodo benzyl guanidine) is a chemical that is readily picked up by many phaeos. When the MIBG is combined with a mildly radioactive agent and injected via a vein in the arm, it sticks to the tumour cells which light up on the screen as radioactive hotspots.

PET imaging:

a PET (positron emission tomography) scan is another nuclear medicine imaging technique similar to MIBG but which uses different agents that can either bind or be taken up by the tumour. Currently, MIBG remains the nuclear medicine imaging standard, however, as more research is done this may change.

What is the treatment?

Treatment depends on many factors such as the location of the tumour and whether it has spread. Most phaeos are benign, especially those occurring in patients with MEN-2. This means they are not cancerous and do not spread. If it is possible to remove the tumour completely, this may be the only treatment required. Surgery usually involves the removal of the entire adrenal gland and is called an adrenalectomy. If your phaeo is believed to be cancer and it has spread locally, then the surgeon will remove the tissues immediately around the adrenal gland and the nearby lymph nodes. If one adrenal gland is removed, then the other gland will produce enough hormones such that you will not need to take medication. However, if both adrenal glands are removed, then you will need life-long medication in the form of steroids to replace the hormones that the adrenal glands would normally make.

Due to the potential for sudden dangerous spikes in blood pressure caused when phaeos are handled during surgery, patients are given special blood pressure medications before surgery. This will sometimes be done as an inpatient. Also occasionally radionuclide therapy may be used to control symptoms.

SURGERY

This depends on the size of the tumour, and whether one or both adrenal glands are being removed. Most tumours can be removed laparoscopically, which means using minimally invasive keyhole surgery performed via a series of small incisions in the abdomen. Some larger tumours may be removed either through a single incision in the abdomen or through the back removing a lower rib.

Some expressions you may hear are:

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:
the removal of both adrenal glands at the same time.

Phaeos can cause very unstable blood pressure during and after surgery. To help stabilize this you will be given medication (anti-hypertensive drugs) called alpha- and sometimes also beta-blockers for at least 10 days before surgery. This practise of controlling the blood pressure is done even for patients with little or no symptoms in order to minimize any risk during surgery. Following surgery the blood pressure should return to normal.

TARGETED RADIONUCLIDE THERAPY

If surgery is not an option, targeted radioactive therapy using I^{131}-MIBG is sometimes an option. As 90% of these tumours are positive to an MIBG scan, they are often suitable for this type of targeted therapy. You may have already had an MIBG scan during the tests requested by your doctor to help assess your symptoms and make the diagnosis.

If you are MIBG-positive it means that your tumour is receptive to this chemical – in other words it has special receptors on its surface which take up the MIBG. MIBG can also be used as a treatment, and is one of the so-called radionuclide therapies. MIBG combined with a much higher dose of radioactivity than that used for the scan is injected into a vein in your arm via a cannula (a thin plastic tube). It takes approximately 40 minutes to complete the very slow injection (also known as an infusion). The radioactive chemical sticks to the MIBG receptors on the tumours cells and works to kill them off while causing no harm to the healthy cells.

Instead of MIBG therapy occasionally some patients have been treated with other radionuclide therapies. This has only really occurred in a few cases and is not currently standard practice.

CHEMOTHERAPY

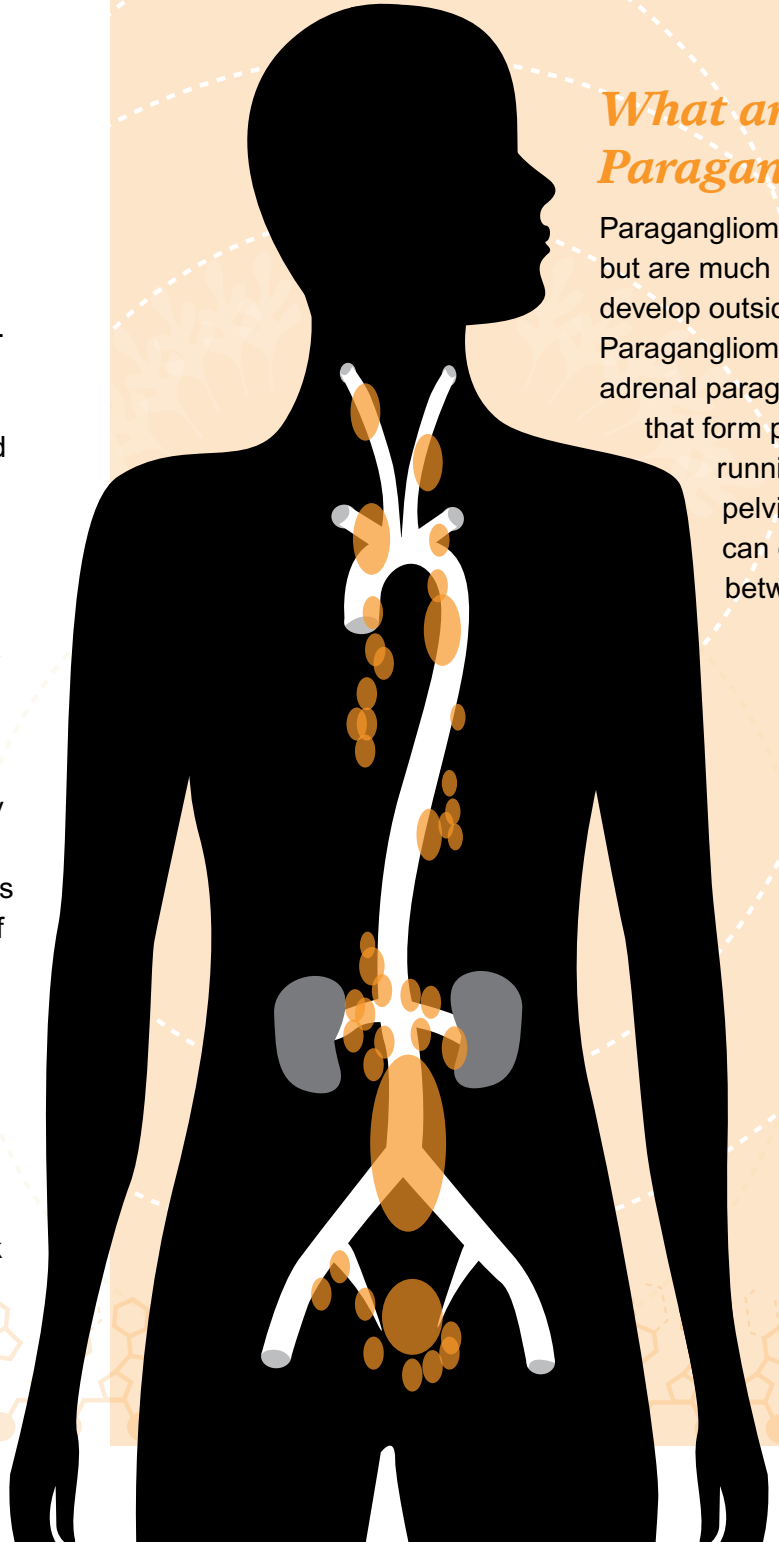
There is a role for chemotherapy in some patients with malignant tumours that are not suitable for radionuclide therapy or in whom the tumour is growing more quickly and so chemotherapy may work better. The chemotherapy medications used can have side effects and this will be discussed in detail with you prior to considering this therapy.

NEWER THERAPIES

A number of new therapies called multi-targeted receptor tyrosine kinase inhibitors (e.g. sunitinib) are becoming more readily available for the treatment of metastatic disease.

Inherited Phaeochromocytomas

In about 1 in 4 phaeo patients, the tumour may be associated with a genetic syndrome e.g.multiple endocrine neoplasia type 2 (MEN2). Patients with MEN2 have a 50% risk of phaeos and almost all will also develop cancer of the thyroid gland in the neck (medullary thyroid cancer). Rarely tumours may occur in the parathyroid glands that lie close to or within the thyroid gland. Initial treatment for MEN2 is for medullary thyroid cancer and consists of the removal of the thyroid gland and surrounding lymph nodes, usually in early childhood. Subsequent management for the other growths associated with MEN2 consists of the monitoring of hormone levels using blood and urine tests, and scans of the neck and abdominal area, sometimes leading to treatment in the form of surgical removal of the tumour and/or affected gland. See separate AMEND Patient Information Book on MEN2.



What are Paragangliomas?

Paragangliomas are similar to phaeos but are much less common and develop outside of the adrenal glands. Paragangliomas arise from the extra-adrenal paraganglia, which are cells that form part of the nervous system running from the neck to the pelvis, and therefore, tumours can develop anywhere between these two points.

Treatment for Paragangliomas

The management plan is similar to that of phaeos. If surgery can be done to remove as much of the tumour as possible then this should be performed. As with phaeos, patients with functioning (hormone-secreting) tumours are given anti-hypertensive medications prior to surgery to reduce the risks of changes in blood pressure during the procedure.

If surgery is not an option or there is some left over tumour that surgeons are not able to remove then these patients can also be considered for treatment with MIBG therapy. It is again dependent on how well the MIBG is taken up by the tumour cells.

Inherited Paraganglioma Syndromes

It is only relatively recently that four types of hereditary paraganglioma syndromes have been identified caused by gene changes in the succinate dehydrogenase (SDH) enzyme. These gene changes are inherited in an autosomal dominant fashion so that a person with the mutation has a 1 in 2 or 50% chance of passing the mutation on to each child.

SDHD and SDHAF2: Whilst these gene changes are inherited in the autosomal dominant manner, individuals will only develop paragangliomas if the change is inherited from their father. They can inherit the mutation from their mother, but will not develop paragangliomas although they can still pass it to their children. Therefore, if a man inherits a gene change from his mother, he will not develop paragangliomas, but if he passes that gene change to his child, that child may develop growths. Individuals with changes in these genes have about a 70% chance of developing growths if inherited from their father. These growths are typically in the head and neck region. Although these tumours usually do not produce hormones, large tumours may cause symptoms such as coughing, hearing loss in one ear, or difficulty swallowing.

SDHC and SDHB: these gene changes can be inherited from either parent.

SDHC patients typically develop paragangliomas in the head or neck region that do not usually produce hormones, although large tumours may cause symptoms such as coughing, hearing loss in one ear, or difficulty swallowing. About 70% of people with the gene change may develop growths.

SDHB patients frequently develop extra-adrenal paragangliomas in the abdomen and thorax and have a higher risk of their tumours being cancerous and spreading (metastasizing). Like phaeos, these tumours may secrete hormones called catecholamines that may cause symptoms such as high blood pressure, rapid heartbeat, headaches or sweating. Less commonly these patients may also develop paragangliomas in the head and neck region, as well as kidney and thyroid cancer (papillary thyroid cancer). Only about 40-60% of people with the gene change will develop paragangliomas/ phaeochromocytomas.

In addition, all patients with SDH gene changes are at risk of developing adrenal gland phaeochromocytomas. Screening for patients with a known SDH gene change or those at 50% risk of inheriting the mutation will undergo similar screening to phaeo patients, including 24 urine collections (or plasma metanephrines and normetanephrines) from around the age of 5 years, annual abdominal ultrasound or MRI scans from around 7 years and neck/thorax/abdominal MRI every 3 years from age 15. The first treatment of choice is usually

surgery.

Medications

To control blood pressure, drugs called alpha-blockers are commonly used; however, other blood pressure medications may also be required.

If both adrenal glands are removed or you become deficient in the hormones released from the adrenal glands, you will require life-long treatment with replacement steroids (corticosteroids). The two main drugs that a patient must take are hydrocortisone and fludrocortisone. They replace the cortisol and another hormone called aldosterone, which are normally 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.

Useful Organisations

AMEND
International patient group providing free information and support to anyone affected by multiple endocrine neoplasia disorders and associated endocrine tumours as well as running a Research Registry and Fund
Tel: +44 (0)1892 516076
Email: info@amend.org.uk
www.amend.org.uk
Membership is FREE

NET Patient Foundation
National charity supporting and educating patients and families affected by neuroendocrine tumours
Tel: +44 (0)800 434 6476
www.netpatientfoundation.org

Authors

- Dr Raj Srirajaskanthan MD, MRCP (for NET Patient Foundation)
- Mrs Jo Grey, CEO (for AMEND)

AMEND UK Medical Advisory Team

- Professor Rajesh Thakker, University of Oxford, Oxford Centre for Diabetes, Endocrinology & Metabolism;
- Dr Caroline Brain, Consultant Paediatric Endocrinologist, UCLH/ GOSH, London;
- Professor John Connell, Dean of Medicine, University of Dundee
- Professor Ashley Grossman, University of Oxford, Oxford Centre for Diabetes, Endocrinology & Metabolism;
- Mr Barney Harrison, Endocrine Surgery, Royal Hallamshire Hospital, Sheffield
- Dr Fiona Lalloo, Consultant Clinical Geneticist, St Mary's Hospital, Manchester;
- Mr Tom Lennard, Professor of Surgery, The Medical School, University of Newcastle upon Tyne
- Mr David Scott-Coombes, Department of Surgery, University Hospital of Wales, Cardiff;

Afterword

This book has been written for patients by patients with the help of a medical advisory team. The aim of this book is to answer those questions, sometimes in great detail, which one may come across before, during and after a diagnosis of phaeochromocytoma or paraganglioma tumours. It is not for use in self-diagnosis. It contains detailed information on tests, surgery and potential symptoms associated with phaeochromocytomas and paragangliomas. However, it is possible that not all of this information will be relevant to you. This book is not intended to replace clinical care decisions and you should always discuss any concerns you have with your specialist. Every care has been taken to ensure that the information contained in this book is accurate, nevertheless, AMEND cannot accept responsibility for any clinical decisions.