Published in final edited form as:

Acta Physiol (Oxf). 2008 February ; 192(2): 325–335. doi:10.1111/j.1748-1716.2007.01809.x.

Diseases of the adrenal medulla

M. M. Fung, O. H. Viveros, and D. T. O'Connor

Departments of Medicine and Pharmacology and Center for Human Genetics and Genomics, University of California at San Diego, La Jolla, CA, USA

Abstract

The adrenal glands are vital in the organism's response to environmental stress. The outer cortex releases steroid hormones: glucocorticoids, mineralocorticoids and sex hormones, which are crucial to metabolism, inflammatory reactions and fluid homeostasis. The medulla is different developmentally, functionally and structurally. It co-releases catecholamines (primarily adrenaline and to some extent noradrenaline) as well as peptides by the all-or-none process of exocytosis from chromaffin granules, to aid in blood pressure and blood flow regulation, with regulated increments during the activation of the sympathetic nervous system. The co-released peptides function to regulate catecholamine release, blood vessel contraction and innate immune responses. Pathology within the adrenal medulla and the autonomic nervous system is primarily because of neoplasms. The most common tumour, called pheochromocytoma when located in the adrenal medulla, originates from chromaffin cells and excretes catecholamines, but may be referred to as secreting paragangliomas when found in extra-adrenal chromaffin cells. Neoplasms, such as neuroblastomas and ganglioneuromas, may also be of neuronal lineage. We will also briefly discuss the catecholamine deficiency state.

Keywords

adrenal; catecholamine; chromaffin; pheochromocytoma

Anatomy and physiology

The adrenal medulla is the location of the majority of the organism's chromaffin cells, derived embryologically from neuroectoderm; ganglion cells and sustentacular cells are also found in the medulla. Chromaffin cells, which store catecholamines in secretory vesicles also known as chromaffin granules, are found in clusters (or nests) and in trabeculae, whereas the ganglion cells are found singly or in clusters interspersed among the chromaffin cells or in association with nerve fibres. The sustentacular cells, or support cells, are located at the periphery of clusters of chromaffin cells.

The precursor chromaffin cells differentiate at the centre of the adrenal gland in response to the glucocorticoid cortisol. A minority of these cells also migrate to form paraganglia, collections of chromaffin cells on both sides of the aorta, the largest of which is primarily found at the origin of the inferior mesenteric artery or at the bifurcation of the aorta and is referred to as the organ of Zuckerkandl.

Correspondence: D. T. O'Connor, Departments of Medicine and Pharmacology, Center for Human Genetics and Genomics (CHGG), University of California at San Diego, Skaggs (SSPPS) room 4256, 9500 Gilman Drive, La Jolla, CA 92093-0838, USA. E-mail: doconnor@ucsd.edu.

Conflict of interest

There are no conflicts of interest for any of the authors for this paper.

The catecholamines are discharged from the chromaffin granules and sympathetic axons by the process of exocytosis, wherein all soluble components of the granule, including enzymes and chromogranins and bioactive peptides, are co-released into the extracellular space, and eventually reach the circulation.

Neuronal uptake (reuptake) is the major route of catecholamine removal from synaptic clefts, although some non-neuronal uptake may be mediated by the organic cation transporter family. After neuronal uptake, cytosolic catecholamines can be either retransported into storage vesicles or deaminated and metabolized through *O*-methylation (by catechol *O*-methyltransferase) or oxidation (by the monoamine oxidases). The liver, with the enzyme alcohol dehydrogenase, is required for the complete degradation of catecholamines to vanillylmandelic acid (VMA). In the blood stream, catecholamines have a very short half-life of only 1–2 min. They are cleared from the circulation largely by neuronal uptake, but in addition are subject to direct renal excretion or sulphaconjugation of a ring hydroxyl group in the gastrointestinal tract (O'Connor, 2003).

Diseases of the adrenal medulla

Pathology within the adrenal medulla and the autonomic nervous system is primarily because of neoplasms. The most common tumour, called pheochromocytoma when located in the adrenal medulla, originates from chromaffin cells and excretes catecholamines. Those tumours found in extra-adrenal chromaffin cells are sometimes referred to as secreting paragangliomas. Neoplasms may also be of neuronal lineage, such as neuroblastomas and ganglioneuromas. There have also been reports of neoplastic proliferation of sustentacular cells (Lau *et al.* 2006). We will also briefly discuss the catecholamine deficiency state.

Pheochromocytoma

Pheochromocytoma is a chromaffin cell neoplasm that typically causes symptoms and signs from episodic catecholamine release, including paroxysmal hypertension. The tumour is an unusual cause of hypertension and accounts for approx. 0.1–0.2% of hypertension cases. In population-based cancer studies, its frequency is approximately two cases per million of the population. The diagnosis of pheochromocytoma is typically made in the fourth or fifth decade of life without gender differences, although, in the approx. 10% of diagnoses which are made in children, there is male predominance. Autopsy series indicate that the incidence of pheochromocytoma increases progressively with age and that as many as 50–75% of pheochromocytomas may be undiagnosed during life, thus suggesting that many pheochromocytomas do not give rise to classic symptomatic features.

About 90% of pheochromocytomas exist as solitary, unilateral and encapsulated adrenal medullary tumours. About 10% are bilateral pheochromocytomas, which are more commonly seen in familial syndromes, where 40–70% of members may have the bilateral tumours. The tumours are vascular, although large ones may contain internal hemorrhagic or cystic areas. About 10% of tumours are extra-adrenal (paragangliomas), of which ~90% are intra-abdominal, often arising from chromaffin cells near the aortic bifurcation in the organ of Zuckerkandl or near the kidney. Other sites include the paravertebral sympathetic ganglia, the urinary bladder, other autonomic ganglia (celiac, superior or inferior mesenteric), the thorax (including the posterior mediastinum, the heart and paracardiac regions) and the neck (in sympathetic ganglia, the carotid body, cranial nerves or the glomus jugulare). Bilateral and extra-adrenal tumours are more common in children.

Fewer than 10% of the tumours are malignant, which is more common among extra-adrenal tumours. The 'rule of 10s' is useful to recall approximate frequencies of pheochromocytoma

that vary from the usual: 10% bilateral, 10% extra-adrenal, 10% malignant, 10% pediatric and 10% without blood pressure elevation (O'Connor, 2003).

Familial pheochromocytoma

Familial pheochromocytomas, typically part of syndromes, are more frequently bilateral, although less commonly malignant. They were previously felt to account for only ~10% of tumours, but in some centres may represent ~25–30% of cases (Opocher *et al.* 2006). A careful family history is essential, and relatives of patients with the familial syndromes, including Von Hippel–Lindau syndrome (VHLS), multiple endocrine neoplasms (MEN) types 2A and 2B and hereditary neurofibromatosis should be screened for pheochromocytoma (Table 1).

Von Hippel–Lindau syndrome is an autosomal-dominant disorder resulting from germline mutations at the *VHL* tumour suppressor locus on chromosome 3p25–p26. Its manifestations include pheochromocytoma (in about 14%), retinal angioma, cerebellar haemangioblastoma, renal cysts and carcinoma, pancreatic cysts and epididymal cystadenoma. Pheochromocytoma occurs only in cases of type 2 VHLS, in which missense mutations (especially Arg238Trp or Arg238Gln) lie in a region of the *VHL* gene product that binds transcriptional elongation factors, and do not occur in type 1 VHLS, which is caused by deletion or premature termination (nonsense) *VHL* mutations.

The MEN types 2A and 2B (Sipple's syndrome) are autosomal-dominant disorders arising from germline mutations on chromosome 10q11.2 in the *RET* proto-oncogene, which encodes a neurotrophin co-receptor tyrosine kinase. The features of MEN type 2A include pheochromocytoma (in about 40%), medullary thyroid carcinoma and primary hyperparathyroidism. The features of MEN type 2B include pheochromocytoma, medullary thyroid carcinoma, multiple mucosal neuromas (of the lips, tongue, buccal mucosa, eyelids, conjunctivae, corneas and gastrointestinal tract) and a marfanoid body habitus. *RET* mutations in MEN type 2A affect one of five Cys residues in the juxtamembrane extracellular domain, probably resulting in intermolecular disulfide formation and consequent constitutive activation of the kinase. The most common *RET* mutation in MEN type 2B, Met981Thr, seems to alter the substrate specificity of the kinase.

Hereditary neurofibromatosis, also known as von Recklinghausen's disease, an autosomal-dominant disorder resulting from mutations at the *NF1* (neurofibromin) locus on chromosome 17q11.2, is manifested as neurofibromas and café au lait spots. Less than 5% of patients have pheochromocytoma.

Germline mutations within the genes for the three subunits of the mitochondrial complex III, succinate dehydrogenase (*SDH*), a heterotetrameric complex involved in the Krebs cycle, have been linked to familial pheochromocytoma and paraganglioma syndrome. Inactivating germline mutations of subunit B (*SDHB*) locus on chromosome 1p35–p36 and of subunit D (*SDHD*) on chromosome 11q23 are inherited as auto-somal-dominant traits, although with variable penetrance and maternal imprinting (Benn *et al.* 2006). The genetic defect at the succinate dehydrogenase subunit C (*SDHC*) has not been linked to adrenal pheochromocytomas, but rather head and neck paraganglioma (Schiavi *et al.* 2005). Patients with *SDHD* mutation are most likely to have head and neck paraganglioma and multifocal tumours, whereas those with the *SDHB* are most likely to have extra-adrenal abdominal paraganglioma with higher risks of malignancy (Havekes *et al.* 2007). Inter-individual phenotype variation has been observed in that the same germline mutation, for example *SDHD* Asp92Tyr, has yielded variable clinical phenotypes ranging from subclinical disease to malignant recurrence.

When evaluating 271 subjects presenting with non-syndromic pheochromocytoma without a family history of disease, Neumann *et al.* (2002) found that 25–35% were carriers of mutations at the *RET*, *VHL*, *SDHD* or *SDHB* loci. Recently, a single common pathway has been suggested for all such genetic lesions associated with paraganglioma/pheochromocytoma, which reduces the likelihood of neural crest cell apoptosis (Maxwell 2005). This approach identified a protein, 2-oxoglutarate-dependent prolyl-hydroxylase, EGLN3/PHD3, at the centre of this pathway as a potential culprit for the causation of the familial syndromes, although so far a defect at this locus itself has not been described in pheochromocytoma (Opocher *et al.* 2006).

Despite the occurrence of five germline mutations that lead to pheochromocytoma, the decision for genetic testing should be based on several factors, including those seen in Figure 1, such as family history, age, extra-adrenal sites or bilateral pheochromocytoma.

Clinical symptoms and signs of pheochromocytoma

The classical sign of pheochromocytoma is hypertension, often labile or refractory to treatment. As pheochromocytoma is a potentially curable form of hypertension, which can be life threatening, a high index of suspicion for the diagnosis is imperative, given a suitable clinical presentation. In about 50% of patients, the hypertension is sustained, but otherwise the hypertension tends to be paroxysmal, with relatively normal blood pressure between surges. Paroxysmal signs and symptoms may vary from many times daily to every week or month. The classical triad of symptoms includes headache, diaphoresis and palpitations or tachycardia. In some series, more than 90% of patients have experienced paroxysmal symptoms of one or more of the classic triad. Less common symptoms include anxiety, tremulousness, pain in the chest or abdomen, weakness or weight loss. Orthostatic hypotension is variably observed, and as many as 15–20% of patients may have cholesterol gallstones. Severe constipation or pseudo-obstruction may occur because catecholamines may inhibit peristalsis. Paroxysmal symptoms on micturition or bladder distention, or painless gross haematuria may suggest pheochromocytoma of the bladder, which requires cystoscopy for diagnosis. Patients older than 60 years with pheochromocytoma are most likely to report minor or no symptoms. Presentation may be highly variable and can mimic other diseases.

Pheochromocytomas may occasionally secrete other hormones, such as calcitonin, ACTH, parathyroid hormone or somatostatin, and patients may have symptoms related to their excess. Certain reactions to medications may suggest pheochromocytoma, such that patients may report an increase in blood pressure after receiving particular antihypertensive drugs, such as beta-adrenergic antagonists, or they may experience a remarkable fall in blood pressure after receiving alpha-1-adrenergic antagonists such as prazosin.

Laboratory diagnosis of pheochromocytoma

Biochemical tests

Because 'essential' hypertension is much more common than pheochromocytoma, biochemical evaluation for pheochromocytoma should be selective and be focused on hypertensive subjects who exhibit relevant clues to pheochromocytoma on history, physical examination or screening laboratory evaluation. Results of routine screening tests obtained for other purposes may suggest the diagnosis. Hypertriglyceridaemia and hyperglycaemia are common, and although half of the patients manifest glucose intolerance, frank diabetes is unusual. Lactic acidosis occurs rarely, even without shock. Serum lactate dehydrogenase activity may be elevated from adrenal isoenzyme 3 (O'Connor & Gochman 1983).

Typically, pheochromocytoma is diagnosed by biochemical evidence of overproduction of catecholamines or their metabolites in plasma or urine samples. Lenders *et al.* (2002) reported

(Table 2) sensitivity and specificity for several biochemical tests, and found that plasma-free metanephrines had the most favourable diagnostic profile (with sensitivity of 97–99% and specificity of 82–96%, followed by 24 hour collection for urine-fractionated metanephrines (which has higher specificity at 98% but a lower sensitivity at 90%, Sawka *et al.* 2003). (Creatinine is measured in the same sample as an index of adequacy and completeness of collection). Metanephrines, the metabolites of catecholamines from the enzyme catechol-O-methyl-transferase, are released continuously by the tumour as catecholamines are metabolized, which may account for their more favourable diagnostic profile when compared with unmetabolized catecholamines that are released sporadically or at lower rates (Figure 2).

Artefactual false-positive assay results have been greatly minimized in recent years with the use of more specific assay methods based on the separation of catecholamines and metabolites by high-pressure liquid chromatography or specific enzymatic incorporation of radiolabels. Potential sources of false-positive tests may still result from elevated endogenous catecholamine levels because of stress, medication and ingestions, or diet. Stress reactions as a result of nicotine, trauma, hypoglycaemia, cold or anxiety and pain may elevate catecholamines and thus be observed in plasma and urine tests. Illnesses known to elevate plasma catecholamines include both acute (e.g. myocardial infarction, diabetic ketoacidosis or sepsis) and chronic conditions (e.g. congestive heart failure, anaemia, respiratory failure or hypothyroidism). A dietary ingestion such as coffee may not only induce release of catecholamines, but also one of its ingredients, caffeic acid, may interfere with some assays for catecholamines. Medications can also induce false-positive results, such as acetaminophen, which may interfere with the assay for metanephrines. Also problematic are ingestions of catecholamines (possibly surreptitious), alpha-methyldopa, L-DOPA, labetalol or sympathomimetic amines, which release endogenous catecholamines from their stores and can result in false-positive elevations of catecholamines. False-positive metanephrine elevations may occur from the use of MAO inhibitors or tricyclic antidepressants. Abrupt withdrawal of central alpha-2-agonists, such as clonidine, may cause ‘rebound’ release of catecholamines (Reisch *et al.* 2006).

To minimize false-positive results, plasma catecholamines are best sampled from a resting and fasting patient who is lying supine with an indwelling antecubital venous cannula in place for at least 15 minutes. Factors that diminish plasma catecholamines include drugs (clonidine, reserpine and alpha-methylparatyrosine), autonomic neuropathy and congenital deficiency of dopamine beta-hydroxylase activity.

Sampling plasma or performing urine biochemical tests during a paroxysmal attack of hypertension is valuable. Because only extreme elevations of plasma noradrenaline perturb blood pressure, the finding of normal plasma catecholamines while blood pressure is elevated argues strongly against pheochromocytoma as the cause.

As the other soluble components of the catecholamine storage vesicle core are also released by pheochromocytomas, the plasma concentration of chromogranin A is also elevated in patients with pheochromocytoma (diagnostic sensitivity of ~83%, specificity of ~96%). Chromogranin A is not substantially elevated by acute venipuncture, nor is it affected by drugs used in the treatment or diagnosis of pheochromocytoma (Hsiao *et al.* 1991), including familial pheochromocytoma (Hsiao *et al.* 1990a). Chromogranin A is released by a variety of neuroendocrine secretory vesicles, and therefore plasma concentration may be elevated in other cases of neuroendocrine neoplasia (Taupenot *et al.* 2003). Chromogranin A immunoreactive fragments are retained in patients with renal insufficiency, leading to potential false-positive results (Hsiao *et al.* 1990b). Measurement of chromogranin A is also useful in cases of suspected factitious (or feigned) pheochromocytoma (Kailasam *et al.* 1995).

Pharmacological tests

Pharmacological tests for phaeochromocytoma are generally not necessary because the diagnosis can usually be confirmed by urine and plasma biochemical measurements at rest or during spontaneous blood pressure surges. The clonidine suppression test can be performed if the biochemical tests in a patient with highly suspected phaeochromocytoma are equivocal. Because phaeochromocytoma chromaffin cells, unlike normal adrenal medullary chromaffin cells, are not innervated, catecholamine release from phaeochromocytoma cells is autonomous and not susceptible to manipulation by drugs that decrease efferent sympathetic outflow, such as the central alpha-2-agonist clonidine (Bravo *et al.* 1981). Blood is obtained for plasma catecholamines before and 3 hours after a single oral dose of 0.3 mg of clonidine. In a subject without phaeochromocytoma, plasma noradrenaline should fall to less than 500 pg mL⁻¹ after clonidine. A positive test (failure of catecholamines to decline after clonidine) is sensitive but may not be entirely specific for phaeochromocytoma. Beta-blockers should be discontinued 48 hours before the test as they may diminish circulating noradrenaline clearance.

Imaging: anatomic localization of phaeochromocytoma

Tumour localization should occur only after compelling evidence of catecholamine excess (Pacok *et al.* 2007). The location is crucial to plan the proper surgical route. Ninety-five per cent of phaeochromocytomas are in the abdomen, and the majority of these can be visualized by one of three modalities: computed tomography (CT), magnetic resonance imaging (MRI) or [¹²³I]-meta-iod-obenzylguanidine (MIBG) scintigraphy. Ultrasound may also be utilized in cases where radiation must be minimized, such as in pregnancy, infants and children, but is not optimal for adult patients.

Computed tomography and MRI are highly sensitive, although they are non-specific because they visualize any mass lesion. The advantage of CT scan is its cost effectiveness and high sensitivity of up to ~98% for adrenal tumours when an unenhanced CT is followed by contrast enhanced and delayed contrast-enhanced CT. MRI may be more effective in differentiating adrenal adenoma from phaeochromocytoma.

To complement a CT or MRI, scintigraphy with [¹²³I]-MIBG, a radiolabelled analogue of guanethidine, is highly specific (98%) because of uptake in 85% of pheochromocytomas. MIBG is transported into chromaffin cells by the reuptake cell membrane catecholamine carrier and accumulates in chromaffin cells to confirm tumour tissue that has been localized via CT scan or MRI. It is especially useful for metastatic, recurrent or extra-adrenal tumours. Positron emission tomography (PET) using 6-[¹⁸F]-fluorodopamine, [¹⁸F]-fluorodeoxyglucose, [¹⁸F]-dihydroxyphenylalanine, [¹¹C]-hydroxyephedrine or [¹¹C]-adrenaline have been evaluated as improved localization techniques for undetectable phaeochromocytoma or metastases, but are not yet widely available (Ilias *et al.* 2003).

Differential diagnosis of phaeochromocytoma

Because many conditions can mimic the diagnostic features of phaeochromocytoma, as many as ~90% of patients who have some feature of the tumour will have a different final diagnosis. The differential diagnosis is broad, and includes any medication or disease state that results in elevated catecholamine levels. Medications, especially surreptitious use of adrenaline or isoproterenol, can emulate catecholamine excess. Also withdrawal of clonidine abruptly or ingestion of tyramine-rich foods while taking a monoamine oxidase inhibitor can result in catecholamine surges. Disease states causing or simulating catecholamine excess and hypertension include thyrotoxicosis, acute intracranial disturbances, such as subarachnoid haemorrhage or posterior fossa masses, and hypoglycaemia, especially in the presence of beta-blockade. Damage to carotid sinus baroreceptors by surgery or tumour may result in baroreflex

failure and result in episodic blood pressure and plasma catecholamine surges (Ketch *et al.* 2002). Some patients with symptomatic blood pressure surges have underlying unrecognized emotional trauma.

Pathophysiology and complications of phaeochromocytoma

Although circulating catecholamine excess is the ultimate cause of hypertension in patients with phaeochromocytoma, the correlation of blood pressure with plasma catecholamines is modest. Desensitization to catecholamine effects may contribute to under-diagnosis of the tumour in elderly patients. In addition to catecholamines, phaeochromocytomas also release a number of potentially vasoactive substances that may modify blood pressure or metabolism, such as calcitonin (O'Connor *et al.* 1983), serotonin, vasoactive intestinal polypeptide (Gozes *et al.* 1983), enkephalins (Parmer & O'Connor 1988), atrial natriuretic factor and somatostatin.

Autopsy series of phaeochromocytoma indicate that even clinically unsuspected cases can be lethal. Rarely phaeochromocytoma may initially present in a life-threatening manner, such as in phaeochromocytoma multisystem crisis with multiorgan failure associated with severe hyper- or hypotension, encephalopathy and lactic acidosis. Hypertension in pregnancy caused by a phaeochromocytoma has a high risk of maternal and foetal mortality. Hemorrhagic necrosis in a phaeochromocytoma can present as an acute abdomen (Brouwers *et al.* 2006).

Congestive heart failure may be because of catecholamine cardiomyopathy. This process is generally reversible after tumour removal, and responds to pre-operative alpha-adrenergic blockade. In most patients, however, the degree of myocardial left ventricular hypertrophy on cardiac ultrasonography is similar to that seen in essential hypertension. Hypertensive crises, myocardial infarctions, pulmonary oedema, acute intestinal obstruction, limb ischaemia, seizures or acute renal failure are examples of other sympathetic nervous system emergencies.

Treatment of phaeochromocytoma

Pre-operative preparation and drug treatment

After the diagnosis of phaeochromocytoma has been made, sufficient adrenergic alpha-blockade should be implemented for 1–4 weeks prior to surgical intervention to control blood pressure, prevent hypertensive crisis and allow any catecholamine-induced plasma volume contraction to correct itself. Alpha-blockade is usually accomplished with oral phenoxybenzamine, an irreversible, non-competitive antagonist. The dose is typically 30–80 mg daily, although starting at 5 mg twice daily and titrating upwards, with a maximum of 50–100 mg twice daily. Treatment goals are to normalize blood pressure, prevent paroxysmal hypertension and abolish tachyarrhythmias. Side effects of an adequate phenoxybenzamine dosage include orthostatic hypotension, tachycardia, nasal congestion, dry mouth, diplopia and ejaculatory dysfunction. In patients intolerant of phenoxybenzamine, an alpha-1-selective antagonist, such as doxazosin (at 2–8 mg once daily) or prazosin (at 0.5–16 mg per day with divided two to three times dosing), may be used (O'Connor, 2003).

If blood pressure or tachyarrhythmias, including sinus tachycardia, are not fully controlled by alpha-blockade, beta-blockade is instituted. Alpha-blockade must be undertaken before beta-blockade is instituted to avoid the effects of unopposed vasoconstrictive alpha-1-receptors which will exacerbate the hypertension. The beta-1-selective antagonists atenolol (50–100 mg daily) or metoprolol (50–200 mg daily) or the combined alpha/beta-antagonist labetalol (100–400 mg daily) may be effective. In subjects with contraindications to beta-blockade, lidocaine or amiodarone can be used for tachyarrhythmias.

If combined management with alpha- and beta-adrenergic antagonists is not fully effective, especially in patients with widespread, unresectable malignant pheochromocytoma, the tyrosine hydroxylase inhibitor alpha-methylparatyrosine can be added at an oral dose of 0.25–1.0 g four times daily. Complications of alpha-methylparatyrosine include sedation, fatigue, anxiety, diarrhoea or extra-pyramidal reactions.

For acute management of severe hypertensive crises, either intravenous nitroprusside or phentolamine is effective. If a pressor response is accompanied by tachycardia, the combined alpha/beta-adrenergic antagonist labetalol may be effective. Opiates, narcotic antagonists (such as naloxone), histamine, adrenocorticotrophic hormone, glucagon or indirect sympathomimetic amines (such as phenylpropanolamine or tyramine) should be avoided as they may provoke hypertensive surges by releasing catecholamines from the tumour. Drugs that block catecholamine reuptake, such as tricyclic antidepressants (e.g. desipramine), cocaine or guanethidine, may also worsen hypertension. Dopaminergic antagonists (such as metoclopramide or sulpiride) may result in hypertension and should be avoided.

Operative and perioperative management

At least 90% of pheochromocytomas are benign, and surgical resection typically provides a cure, although up to 25% of patients may retain a lesser degree of hypertension. Several surgical approaches are feasible, depending on the characteristics of the pheochromocytoma and the experience of the surgeon. Laparoscopic adrenalectomy is increasingly used in recent years and may result in faster post-operative recovery. The entire adrenal gland harbouring a pheochromocytoma is usually excised, but during excision of bilateral tumours, a section of cortex from one adrenal gland may be left in place to prevent steroid dependency. Intravenous glucose replacement (5% dextrose) is given to prevent hypoglycaemia, a frequent occurrence after tumour removal. Hypertensive surges are likely to occur during anaesthetic induction, intubation, tumour palpation and ligation of tumour veins. If intra-operative hypotension occurs, the initial treatment is saline infusion to expand intravascular volume. Noradrenaline infusion is appropriate only after plasma volume expansion to euvolaemia.

For intra-operative blood pressure surges, intravenous nitroprusside is often used. Alternatively, acute alpha-blockade can be accomplished with intravenous phentolamine. The calcium channel antagonist nicardipine has also been used.

In the post-operative period, the patient must be monitored for development of hypotension, hypertension and hypoglycaemia. The operative mortality rate of pheochromocytoma resection is now less than 2–3%. Residual tumour may be diagnosed by biochemical testing 1–2 weeks post-operatively. Patients should be followed for at least 10 years post-operatively, because of the small (approx. 5%) risk of late tumour recurrence. Perioperative complications are more frequent in patients with higher blood pressures, higher catecholamine and metabolite excretion, recurrent or multiple surgical excisions or prolonged anaesthesia. Benign pheochromocytomas have a 5-year survival rate greater than 95%, with recurrences less than 10%.

Malignant pheochromocytoma

Although most pheochromocytomas are typically well-encapsulated, localized benign growths, approx. 5–10% are malignant, which is more common among extra-adrenal tumours. Because histopathology is not reliable, malignancy is diagnosed by distant metastatic spread of the tumour, commonly to the bone, lung, lymph nodes or liver. Nearby tissue invasion, such as along adjacent vascular structures like the inferior vena cava, may suggest malignancy but is not diagnostic. Extreme elevations in plasma DOPA, noradrenaline or chromogranin A may suggest malignant pheochromocytoma, such that serial chromogranin A measurements can

be used to monitor tumour response to treatment (Figure 3; Rao *et al.* 2000). Currently, only the presence of *SDHB* gene mutation suggests a high probability of malignant disease, up to 35%.

Therapy for the malignancy is usually surgery, chemotherapy and radiotherapy to debulk the tumour and block endocrine activity. Surgery is not usually curative because of the remaining tumour tissue, but periodic surgical debulking may help control symptoms. Alpha- and beta-adrenergic blockade remains the mainstay of management of the symptoms and signs of catecholamine excess.

Metastases, commonly in the retroperitoneum, skeleton and bone, lymph nodes and liver, tend to be slow growing with a variable natural history. The response to chemotherapy has generally been disappointing, but the combination of vincristine, cyclophosphamide and dacarbazine (CVD) has yielded complete and partial response rates of 57% (Scholz *et al.* 2007). Skeletal metastases have some response to irradiation, although the neoplasm is not particularly susceptible to radiation therapy. High-dose (500 mCi cumulative dose) repeated radiation therapy with intravenous [¹³¹I]-MIBG has been tolerated well and able to be repeated. The individual course of a malignant pheochromocytoma is highly variable, but the long-term 50% survival is less than 5 years.

Paragangliomas

Extra-adrenal pheochromocytomas can be referred to as paragangliomas. They arise from paraganglionic chromaffin cells in association with sympathetic nerves, and are found in the organ of Zuckerkandl, urinary bladder, chest, neck and at the base of the skull. They are more common in children than in adults, and are more frequently malignant. As discussed earlier, mutations in the *SDH* family may predispose to head and neck paragangliomas and pheochromocytoma (Table 1). One series of 128 paragangliomas found that 40% were hyperfunctioning with evidence of catecholamine excess (Erickson *et al.* 2001).

Neuroblastomas

Neuroblastomas and ganglioneuromas are tumours of the primitive neuroblast cells from the sympathetic nervous system in ganglia and the adrenal medulla. They may represent a continuum of neuronal maturation and are the most common malignancy found in children, representing ~7–10% of all childhood cancers. For neuroblastomas, the median age of diagnosis is 18 months, with approx. 65% found in the abdomen with the adrenal medulla as the most common site. Over 50% have metastatic disease at presentation and over 90% have elevated catecholamines, but only rarely are there presenting emergency symptoms because of the excess catecholamines similar to those seen with pheochromocytoma, such as hypertensive encephalopathy or cardiac failure. Subjects may also have paraneoplastic phenomena such as secretory diarrhoea from vasoactive intestinal peptide. Chromogranin A elevation parallels neuroblastoma disease stage (Hsiao *et al.* 1990c).

Because of their more mature ganglion cells which are histologically benign, ganglioneuromas are often metabolically inactive and asymptomatic. They are found incidentally or with compressive symptoms mostly in the posterior mediastinum or retroperitoneum. In a case series of 49 pediatric and young adult subjects, diagnosed at a mean age of 79 months (aged 18 months to 26 years), lesions showed a propensity towards extra-adrenal locales (79% vs. 21%) (Georger *et al.* 2001). Approx. 40% of subjects had evidence of catecholamine excess. Although some metabolic activity has been detected in a portion of these tumours, either positive scintigraphy scans or elevated catecholamine levels in the plasma and urine, this was not associated with malignancy or recurrence of tumour.

Catecholamine deficiency disease states

Congenital absence of the adrenal cortex may cause a developmental absence of the adrenal medulla. Loss of both adrenal glands seldom produces a catecholamine deficiency state, probably because of production of catecholamines in the autonomic nervous system (sympathetic neuronal noradrenaline). An example where the deficiency is noticeable is in diabetic patients receiving insulin. In the state of hypoglycaemia, catecholamines are necessary to trigger hepatic glycogenolysis as the usual counter-regulatory response. If autonomic neuropathy is present, then deficient adrenaline release during hypoglycaemia may result in impairment and prolong its duration.

Several individuals in America and Europe have been described with hereditary deficiency of dopamine beta-hydroxylase. They have greatly diminished or undetectable noradrenaline and adrenaline levels in blood, urine and cerebrospinal fluid. The initial features of this lifelong syndrome include severe orthostatic hypotension, ptosis, nasal stuffiness, hyperextensible joints and retrograde ejaculation. The diagnosis is made in patients with severe orthostatic hypotension, a plasma noradrenaline/dopamine ratio of less than 1, and undetectable plasma dopamine beta-hydroxylase enzymatic activity and immunoreactivity. With sympathetic activation in these subjects, the sympathetic axons release the precursor dopamine instead of noradrenaline, which may worsen hypotension. The molecular basis of this disorder reportedly included compound heterozygosity for inactivating mutations at the *DBH* locus (Kim *et al.* 2002).

Conclusions

Diseases of the adrenal medulla and chromaffin cells are fortunately rare and few in number, but they are potentially life threatening. Diagnosis requires a high index of suspicion and careful workup to rule out other sources of elevated catecholamines prior to diagnosis. With the recent discovery of new germline mutations for familial syndromes and the increasing identification of them in seemingly 'sporadic' pheochromocytoma, thorough family histories and screenings need to be performed. Future directions should include investigation of the germline mutations and improved early detection and treatment of pheochromocytoma and paraganglioma, especially in malignancy.

Acknowledgements

National Institutes of Health, Department of Veterans Affairs supported this study.

References

- Benn DE, Gimenez-Roqueplo AP, Reilly JR, et al. Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. *J Clin Endocrinol Metab* 2006;91:827–836. [PubMed: 16317055]
- Bravo EL, Tarazi RC, Fouad FM, et al. Clonidine suppression test: a useful aid in the diagnosis of pheochromocytoma. *N Engl J Med* 1981;305:623–626. [PubMed: 7266587]
- Brouwers FM, Eisenhofer G, Lenders JWM, Pacak K. Emergencies caused by pheochromocytoma, neuroblastoma, or ganglioma. *Endocrinol Metab Clin N Am* 2006;35:699–724.
- Erickson D, Kudva YC, Ebersold MJ, et al. Benign paragangliomas: clinical presentation and treatment outcomes in 236 patients. *J Clin Endocrinol Metab* 2001;86:5210–5216. [PubMed: 11701678]
- Georger B, Hero B, Harms D, Grebe J, Scheldhauer K, Berthold F. Metabolic activity and clinical features of primary ganglioneuromas. *Cancer* 2001;91:1905–1913. [PubMed: 11346873]
- Gimenez-Roqueplo AP, Lehnert H, Mannelli M, et al. Pheochromocytoma, new genes and screening strategies. *Clin Endocrinol* 2006;65:699–705.

- Gozes I, O'Connor DT, Bloom FE. A possible high molecular weight precursor to vasoactive intestinal polypeptide sequestered into pheochromocytoma chromaffin granules. *Regul Pept* 1983;6:111–119. [PubMed: 6878752]
- Havekes B, Corssmit EPM, Jansen JC, van der Mey AGL, Vriends AHJT, Romijn JA. Malignant paragangliomas associated with mutations in the succinate dehydrogenase D gene. *J Clin Endocrinol Metab*. 2007[published ahead of print.]
- Hsiao RJ, Neumann HPH, Parmer RJ, Barbosa JA, O'Connor DT. Chromogranin A in familial pheochromocytoma: diagnostic screening value, prediction of tumor mass, and post-resection kinetics indicating two-compartment distribution. *Am J Med* 1990a;88:607–613. [PubMed: 2189303]
- Hsiao RJ, Mezger MS, O'Connor DT. Chromogranin A in uremia: progressive retention of immunoreactive fragments. *Kidney Int* 1990b;37:955–964. [PubMed: 2313983]
- Hsiao RJ, Seeger RC, Yu AL, O'Connor DT. Chromogranin A in children with neuroblastoma. Serum concentration parallels disease stage and predicts survival. *J Clin Invest* 1990c;85:1555–1559. [PubMed: 2332506]
- Hsiao RJ, Parmer RJ, Takiyuddin MA, O'Connor DT. Chromogranin A storage and secretion: sensitivity and specificity for the diagnosis of pheochromocytoma. *Medicine (Baltimore)* 1991;70:33–45. [PubMed: 1988765]
- Ilias I, Yu J, Carrasquillo JA, et al. Superiority of 6-[18-F] fluorodopamine positron emission tomography versus [131-I] metaiodobenzylguanidine scintigraphy in the localization of metastatic pheochromocytoma. *J Clin Endocrinol Metab* 2003;88:4080–4087. [PubMed: 12970266]
- Kailasam MT, Parmer RJ, Stone RA, et al. Factitious pheochromocytoma: novel mimicry by valsalva maneuver and clues to diagnosis. *Am J Hypertens* 1995;8:651–655. [PubMed: 7662252]
- Ketch T, Biaggioni I, Robertson R, Robertson D. Four faces of baroreflex failure: hypertensive crisis, volatile hypertension, orthostatic tachycardia, and malignant vagotonia. *Circulation* 2002;105:2518–2523. [PubMed: 12034659]
- Kim CH, Zabetian CP, Cubells JF, et al. Mutations in the dopamine beta-hydroxylase gene are associated with human norepinephrine deficiency. *Am J Med Genet* 2002;108:140–147. [PubMed: 11857564]
- Lau SK, Romansky SG, Weiss LM. Sustentaculoma: report of a case of a distinctive neoplasm of the adrenal medulla. *Am J Surg Pathol* 2006;30:268–273. [PubMed: 16434904]
- Lenders JWM, Pacak K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA* 2002;287:1427–1434. [PubMed: 11903030]
- Maxwell PH. A common pathway for genetic events leading to pheochromocytoma. *Cancer Cell* 2005;8:91–93. [PubMed: 16098460]
- Neumann HPH, Bausch B, McWhinney SR, et al. Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med* 2002;346:1459–1466. [PubMed: 12000816]
- O'Connor, DT. The adrenal medulla, catecholamines, and pheochromocytoma. In: Cecil, RL.; Goldman, L.; Ausiello, DA., editors. *Cecil's Textbook of Medicine*. Philadelphia, PA: Saunders; 2003. p. 1419-1424.
- O'Connor DT, Gochman N. Lactic dehydrogenase activity in human pheochromocytoma. *JAMA* 1983;249:383–385. [PubMed: 6848829]
- O'Connor DT, Frigon RP, Deftos LJ. Immunoreactive calcitonin in catecholamine storage vesicles of human pheochromocytoma. *J Clin Endocrinol Metab* 1983;56:582–585. [PubMed: 6822655]
- Opochnier G, Schiavi F, Iacobone M, et al. Familial nonsyndromic pheochromocytoma. *Ann NY Acad Sci* 2006;1073:149–155. [PubMed: 17102081]
- Pacak K, Eisenhofer G, Ahlman H, et al. Pheochromocytoma: recommendations for clinical practice from the First International Symposium. *Nat Clin Pract Endocrinol Metab* 2007;3:92–102. [PubMed: 17237836]
- Parmer RJ, O'Connor DT. Enkephalins in human pheochromocytomas: localization in immunoreactive, high molecular weight form to the soluble core of chromaffin granules. *J Hypertens* 1988;6:187–198. [PubMed: 3361117]
- Rao F, Keiser HR, O'Connor DT. Malignant pheochromocytoma. Chromaffin granule transmitters and response to treatment. *Hypertension* 2000;36:1045–1052. [PubMed: 11116123]
- Reisch N, Peczkowska M, Januszewicz A, Neumann HPH. Pheochromocytoma: presentation, diagnosis, and treatment. *J Hypertens* 2006;24:2331–2339. [PubMed: 17082709]

- Sawka AM, Jaeschke R, Singh RJ, Young WF. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. *J Clin Endocrinol Metab* 2003;88:553–558. [PubMed: 12574179]
- Schiavi F, Boedeker CC, Bausch B, et al. Predictors and prevalence of paraganglioma syndrome associated with mutations of the SDHC gene. *JAMA* 2005;294:2057–2063. [PubMed: 16249420]
- Scholz T, Eisenhofer G, Pacak K, Dralle H, Lehnert H. Current treatment of malignant pheochromocytoma. *J Clin Endocrinol Metab* 2007;92:1217–1225. [PubMed: 17284633]
- Singh RJ. Advances in metanephrine testing for the diagnosis of pheochromocytoma. *Clin Lab Med* 2004;24:85–103. [PubMed: 15157558]
- Taupenot L, Harper KL, O'Connor DT. The chromogranin-secretogranin family. *N Engl J Med* 2003;348:1134–1149. [PubMed: 12646671]

Figure 1.

Algorithm for genetic testing in pheochromocytoma and paraganglioma. The algorithm is recommended by European Network for the Study of Adrenal Tumours (ENS@T) Pheochromocytoma Working Group. Reproduced from Gimenez-Roquelo *et al.* (2006). Pheochromocytoma, new genes and screening strategies. *Clin Endocrinol* 65, 699–705. For definitions of abbreviations and acronyms, see Table 1.

Figure 2.

Metanephrines in phaeochromocytoma. The detection of free metanephrines in plasma and conjugated metanephrines in urine has the highest sensitivity and specificity for diagnosis of phaeochromocytoma. COMT, catechol *O*-methyltransferase. Reprinted from Singh (2004) with permission from Elsevier.

Figure 3.

Plasma concentrations of chromaffin granule transmitters (chromogranin A, noradrenaline or adrenaline) in subjects with phaeochromocytoma ($n = 27$) stratified by tumour behaviour, benign ($n = 13$) vs. malignant ($n = 14$). Individual values are from samples obtained before treatment. P -values refer to comparisons of benign vs. malignant disease. Normal ranges: chromogranin A 48 ± 3 ng mL⁻¹; noradrenaline 200 ± 7.8 pg mL⁻¹; adrenaline 18 ± 1.5 pg mL⁻¹. From Rao *et al.* (2000).

Table 1
Hereditary syndromes associated with pheochromocytoma and paraganglioma

Syndrome	Hereditary pattern	Clinical phenotype	Risk of pheochromocytoma (%)	Mutated germ line locus	Chromosome
Familial pheochromocytoma-paraganglioma syndrome (PGL1)	AD with incomplete penetrance because of maternal imprinting	Head and neck paraganglioma, extra-adrenal abdominal paraganglioma, pheochromocytoma	7–50 (estimated)	<i>SDHD</i>	11q21–q23
Familial pheochromocytoma-paraganglioma syndrome (PGL4)	AD with incomplete penetrance	Extra-adrenal abdominal paraganglioma, head and neck paraganglioma, pheochromocytoma	18–28 (estimated)	<i>SDHB</i>	1p35–p36
Familial pheochromocytoma-paraganglioma syndrome (PGL3)	AD with incomplete penetrance	Parasympathetic paraganglioma	None	<i>SDHC</i>	1q21
MEN-2A	AD	Medullary carcinoma of the thyroid, hyperparathyroidism	50	<i>RET</i> (proto-oncogene)	10q11.2
MEN-2B	AD	Medullary carcinoma of the thyroid, multiple mucosal neuromas, marfanoid, hyperparathyroidism	50	<i>RET</i> (proto-oncogene)	10q11.2
Neurofibromatosis type I	AD	Neurofibromas of peripheral nerves, café au lait spots	1	<i>NF1</i>	17q11.2
Von Hippel–Lindau (VHL) syndrome	AD	Retinal angioma, CNS haemangioblastoma, renal cell cancer, pancreatic and renal cysts	14	<i>VHL</i>	3p25–p26

AD, autosomal dominant. MEN, multiple endocrine neoplasia.

Table 2
Sensitivity and specificity of plasma and urine biochemical tests for
phaeochromocytoma

	Sensitivity		Specificity	
	Hereditary (%)	Sporadic (%)	Hereditary (%)	Sporadic (%)
Plasma				
Free metanephrines	97	99	96	82
Catecholamines	69	92	89	72
Urine				
Fractionated metanephrines	96	97	82	45
Catecholamines	79	91	96	75
Total metanephrines	60	88	97	89
Vanillylmandelic acid	46	77	99	86

From Lenders *et al.* (2002).