Pheochromocytoma

INTRODUCTION

Pheochromocytoma is a catecholamine-secreting tumor with a wide spectrum of presentations ranging from minimal symptoms (1) to sudden death (2). While early diagnosis can lead to a curative treatment course (3), outcomes are often fatal when the condition is unrecognized (4). Pheochromocytoma should be included in the differential diagnosis for patients with poorly controlled hypertension, heart failure, or cerebrovascular events. Furthermore, critical care physicians should be familiar with pheochromocytoma crisis, as it is a medical emergency requiring the highest level of specialty care.

PATHOPHYSIOLOGY

Most pheochromocytomas are benign and do not locally invade or metastasize. The morbidity of pheochromocytoma is primarily related to the adverse cardiovascular effects of unregulated systemic catecholamine excess. Pheochromocytomas originate from chromaffin cells, and by definition, are located in the adrenal medulla. Although extra-adrenal pheochromocytomas are usually referred to as paragangliomas, these terms will be considered synonymous for the purpose of this chapter.

Intermittent and unregulated catecholamine hypersecretion is the hallmark pathophysiologic feature of pheochromocytoma. There are three sequential products synthesized in the adrenal medulla from the precursor L-tyrosine—dopamine, norepinephrine, and epinephrine. The rate-limiting step in catecholamine synthesis is the production of the precursor peptide L-DOPA, a process catalyzed by the enzyme tyrosine hydroxylase. By decarboxylation, L-DOPA is converted to dopamine, which is then converted to norepinephrine by β-hydroxylase. Ultimately, norepinephrine is converted to epinephrine by phenylethanolamine-N-methyltransferase.

While norepinephrine is the predominant catecholamine secreted by most pheochromocytomas, there are reports of rare tumors that secrete dopamine (5), adrenocorticotrophic hormone (6), vasoactive intestinal protein (7), and calcitonin gene–related protein (8). The highly varied presentation of pheochromocytoma may, in part, be explained by the variety of secretory products. Vasoactive intestinal protein can cause abdominal discomfort and a secretory diarrhea. Calcitonin gene–related protein, like vasoactive intestinal protein, is a potent vasodilator that can cause hypotension.

Because phenylethanolamine-N-methyltransferase is found only in the adrenal medulla and the organ of Zuckerkandl, epinephrine-secreting tumors are typically located in these two locations. Although some have suggested that patients in pheochromocytoma crisis have tumors that secrete primarily epinephrine, this has not been substantiated (9).

The diagnostic laboratory tests rely on the detection of the metabolic products of the catecholamines. Carboxyl-O-methyltransferase (COMT) converts norepinephrine to normetanephrine and epinephrine into metanephrine. Monoamine oxidase (MAO) then catalyzes the conversion of metanephrines into vanillylmandelic acid (VMA).

EPIDEMIOLOGY

Pheochromocytoma is a rare tumor with an incidence ranging from 0.1% (10) to 0.25% (11) in large autopsy studies. Based on outpatient studies, the prevalence in hypertensive patients is in the range of 0.1% to 1%. There is no difference in incidence or prevalence between men and women. While most cases are sporadic (12), up to 24% of nonsyndromic pheochromocytoma patients have specific germline mutations, including RET (MEN-2), VHL (von Hippel–Lindau), and succinate dehydrogenase subunits D (SDHD) and B (SDHB) (13). Other even less common germline mutations include TMEM127, MAX, SDHA, SDHC, and SDHAF2.

Approximately 40% of MEN 2 patients develop pheochromocytoma. While bilateral and multicentric tumors are more common in these patients, extra-adrenal and malignant lesions are uncommon. Because of the relatively high incidence of pheochromocytoma, patients known to have the RET oncogene mutation should be routinely screened for elevation in serum or urine metanephrines.

VHL disease is inherited in an autosomal dominant fashion and is characterized by retinal hemangiomas, pancreatic tumors, cerebellar hemangioblastoma, kidney lesions, and epidermal cystadenoma. Pheochromocytoma can be found in up to 20% of people with VHL disease. As in MEN 2, bilateral disease is more common than in sporadic cases.

SDHB and SDHD are susceptibility genes for pheochromocytoma associated with extra-adrenal lesions (14). While SDHD mutation carriers are more likely to have multifocal extra-adrenal pheochromocytomas, SDHB mutation carriers are more likely to develop malignancy and may be associated with renal and thyroid carcinoma.

Other rare familial disorders that are associated with pheochromocytoma include von Recklinghausen’s disease (15) and Carney syndrome (16).

CLINICAL PRESENTATION

The symptoms of pheochromocytoma are highly variable (17), which has earned this tumor the nickname “the great mimic” (18). The classic symptoms include episodic headache, palpitations, diaphoresis, and visual blurring. Other complaints may include tremors, anxiety, dizziness, nausea, diarrhea, abdominal discomfort, Raynaud phenomenon, and weight loss (19).
In addition, observers often note intermittent pallor and weight loss in those affected.

Although pheochromocytomas are often incidentally discovered on radiographic scans performed for other reasons (20), upon specific questioning, many of these patients report symptoms referable to the hyperadrenergic state. Up to 23% of all “incidentalomas” are discovered during abdominal imaging in trauma patients, further underscoring the significance of this tumor in the critical care setting (21). Moreover, among patients with a known history of another malignancy, up to one-fourth of radiologically discovered adrenal tumors are pheochromocytomas and not metastatic disease (22).

Hypertension is the most common feature of pheochromocytoma, and occurs in up to 90% of patients. Patients may be normotensive between surges of catecholamine release, and postural tachycardia and hypotension are not uncommon which may result from hypovolemia, increased production of endogenous vasodilators, or downregulation of α1-adrenergic receptors. Anecdotally reports indicate that peripheral vasoconstriction can be so severe that, on rare occasion, blood pressure cannot be measured with a traditional cuff and sphygmomanometer. Conversely, some patients can be normotensive for many years (23), and only suffer a hypertensive crisis after stress (24). Less commonly, some present with diastolic hypertension and postural hypotension, in the absence of antihypertensive therapy. Notably, some ophthalmologists have reported severe retinopathy, in the absence of antihypertensive therapy. Notably, some ophthalmologists have diagnosed pheochromocytoma by identifying severe retinopathy on routine eye examination in patients without known risk factors. Signs and symptoms of ischemic colitis can also be found in patients with highly functional tumors, presumably from vasoconstriction.

**ESSENTIAL DIAGNOSTIC TESTS**

**Biochemical Identification**

The biochemical diagnosis of pheochromocytoma is dependent upon the detection of elevated levels of catecholamines or their metabolites. Because functional pheochromocytomas release catecholamines heterogeneously and intermittently (25), spot checks of norepinephrine, epinephrine, or dopamine are often within a normal range and cannot reliably diagnose pheochromocytoma.

Conversely, plasma metanephrines are continuously elevated in patients with functional pheochromocytomas. Total metanephrine measurement is less sensitive than determining the fractionated normetanephrine, metanephrine, and methoxytyramine, which are the metabolites of norepinephrine, epinephrine, and dopamine. Phlebotomy for plasma metanephrines should be performed with the patient in the supine position.

Plasma free metanephrine measurement is more sensitive than urinary fractionated metanephrines, but is less specific (26). Normal plasma free metanephrines effectively exclude the diagnosis of pheochromocytoma. Plasma and urine metanephrine levels are commonly elevated in critically ill patients and cause false-positive tests. However, extremely high levels in a patient with an adrenal tumor are diagnostic of pheochromocytoma.

Certain medications and radiographic contrast agents can interfere with the laboratory results and should be withheld before testing. The list of medications that can affect the biochemical testing for pheochromocytoma is long and includes acetaminophen, β-blockers, vasodilators, α-blockers, stimulants, antipsychotics, antidepressants, and calcium channel blockers.

When the diagnosis of pheochromocytoma is equivocal, these medications should be held prior to biochemical testing. Provocative tests with agents such as histamine, glucagon, and naloxone are no longer recommended, as they can be dangerous and are ineffective in patients with normal urinary studies (27).

Acute adrenal hemorrhage can cause transient high catecholamine levels in the absence of pheochromocytoma. However, cross-sectional imaging can readily detect hemorrhage, which can be found with or without an adrenal mass.

Marginal elevations in serum metanephrines or urinary fractionated metanephrines are unlikely to be caused by pheochromocytoma, since both tests typically are at least quadrupled in most patients. Pheochromocytoma can be excluded with confidence when both plasma and urine tests are normal in a hypertensive and symptomatic patient. However, it cannot be absolutely excluded in normotensive and asymptomatic patients (28). Borderline results warrant repeat measurement after 30 minutes of supine rest.

**Tumor Localization**

The biochemical diagnosis is essential to diagnose and initiate treatment for the critically ill patient with pheochromocytoma. Tumor localization usually will not change the therapeutic plan for patients in the intensive care unit.

The identification of extra-adrenal pheochromocytoma may not be predictive of malignancy or prognosis (12). However, localization studies are important for surgical planning (29), and can help confirm the diagnosis.

Ultrasound is particularly useful in critically ill patients, as it can be done at the bedside without exposure to nephrotoxic contrast agents or ionizing radiation. Although ultrasound can be performed quickly and can accurately exclude a large adrenal lesion, it is user-dependent with limited sensitivity for small adrenal lesions.

Magnetic resonance imaging (MRI) is an effective way to identify pheochromocytoma lesions and can delineate the anatomy important for surgical planning. Pheochromocytomas have a characteristic high-intensity signal on T2-weighted MR images. The drawbacks of MRI are the high cost, the long procedural times, and the lack of available scanners at some institutions. MRI is ideal for patients with surgical clips that cause artifacts on computed tomography (CT), in patients with an allergy to iodinated contrast agents, and in patients that should not be exposed to ionizing radiation.

CT scans are more common, and subsequently, incidentally discovered adrenal masses are more frequently found by CT scanning. On CT scans, pheochromocytomas typically have a higher density than adenomas and are hypervascular. While most pheochromocytomas occur in the adrenal glands, patients should be scanned from the chest to the pelvis to evaluate for extra-adrenal lesions. Minor drawbacks to consider include the possibility of exacerbating a pheochromocytoma crisis from contrast injection; exposure to ionizing radiation, which may be important in some obstetrical or pediatric patients; and the obscuring artifacts that can occur from implanted devices and surgical clips.

Meta-iodobenzylguanidine (MIBG) is concentrated within adrenergic vesicles, which allow scintigraphic functional
imaging of the whole body. MIBG scanning is not as sensitive as FDG-PET CT for finding extra-adrenal tumors and metastatic disease, but $^{123}$-MIBG scanning is useful to determine whether future high dose $^{131}$-MIBG can be a treatment option.

**Workup of Incidental Lesions**

Subclinical or mild cases of pheochromocytoma are sometimes discovered when incidental lesions are found on CT scans or MR images obtained for other reasons. While many clinicians continue to perform fine-needle aspiration biopsy and selective venous sampling for patients with adrenal tumors, these interventional studies may precipitate a pheochromocytoma crisis and are relatively contraindicated. The finding of an adrenal “incidentaloma” should prompt the biochemical workup described above to exclude the diagnosis of pheochromocytoma. Importantly, pheochromocytoma should be ruled out prior to biopsy of any adrenal mass. Other biochemical studies to consider for incidentally discovered adrenal tumors include the measurement of plasma aldosterone, renin activity, and 24-hour urine cortisol or dexamethasone suppression test. These studies will rule out aldosteronoma and Cushing syndrome. All functioning adrenal lesions, including pheochromocytoma, should be resected electively.

**MANAGEMENT**

**Nonemergent Pheochromocytoma**

Pheochromocytoma is a rare cause of cardiovascular emergencies such as heart failure (30), myocardial infarction (31), and stroke (32). When pheochromocytoma is the cause of these events, appropriate therapy to control the hyperadrenergic state can often reverse or minimize disability. Most patients with pheochromocytoma who succumb to myocardial infarction or cerebrovascular catastrophe have undiagnosed tumors (4).

Although surgical intervention remains the only curative therapy for pheochromocytoma, the tumor should be resected only after appropriate preoperative steps are undertaken. Preoperative preparation for elective resection includes α-blockade to control hypertension, prevent cardiac arrhythmias, and allow adequate volume resuscitation before resection. Effective preoperative preparation and α-blockade reduce operative mortality (33). Even in the normotensive patient, appropriate α-blockade will prevent hemodynamic instability caused by operative stress and tumor manipulation during elective resection.

Phenoxybenzamine is an excellent α-blocker for preoperative patients because it has a relatively long half-life. The starting dose is 10 mg every 12 hours and should be titrated upwards, as tolerated. Alternatively, doxazosin may also be used, and is often less expensive than phenoxybenzamine. The highest tolerable level of blockade is preferable, and dose escalation can be halted when the patient has postural hypotension. Most patients complain of nasal congestion during adequate α-blockade, but this need not prompt adjustment in dosage. Patients should have their heart rate and blood pressure checked after lying for more than 5 minutes, then after 1-minute standing. This routine should be repeated at least twice daily and when the patient has symptoms, to direct dose adjustment. Increased consumption of salty foods, or less commonly used, saline infusion, can help minimize orthostasis and improve the degree of α-blockade. The dose escalation should be stopped when the heart rate increases greater than 20 beats/min or if the systolic blood pressure falls more than 15, after standing for a minute.

Dihydropyridine calcium channel blockers (e.g., amlodipine, nifedipine, nicardipine) can also be used to attenuate the cardiovascular response to catecholamine surge (34). Some studies comparing calcium channel blockers to α-blockers showed no significant difference in hemodynamic stability and outcomes (35,36). Although the experience with α-blockade is more extensive in most centers, calcium channel blockers can also be used to attenuate hemodynamic instability before and during surgery.

Additionally, β-blockers are sometimes needed to control heart rate before the resection. They should be given only after adequate α-blockade, to avoid severe hypertension from unopposed α-stimulation. Metyrosine, an inhibitor of tyrosine hydroxylase, reduces catecholamine production and can be added to the preoperative regimen (37). Narcotics should generally be avoided, as they may stimulate histamine release, which may in turn trigger a crisis.

Although surgical resection is the only curative intervention for patients with pheochromocytoma, appropriate preoperative measures help to avoid unfavorable events, such as intraoperative hemodynamic instability. α-blockade must be attained before elective resection of pheochromocytoma. β-blockade is used selectively in patients with persistent tachycardia, but only after adequate α-blockade.

**The Postoperative Patient**

Perioperative complications are typically related to inadequate adrenergic blockade, lack of appropriate intravascular volume expansion, or to a technical problem. Surgical complications include bleeding, infection, and damage to nearby structures, such as the spleen or renal vessels. An uncommon surgical complication of adrenalectomy is renovascular hypertension, a result of injury to, or thrombosis of, the upper pole branch of the renal artery. In our experience, pheochromocytoma patients are at an increased risk of deep venous thrombosis and pulmonary embolus after surgery. Thus, deep venous thrombosis prophylaxis should include subcutaneous heparin, sequential compression devices for the lower extremities, and early ambulation.

Most pheochromocytomas smaller than 6 cm can be resected using the laparoscopic technique. Larger tumors may require laparotomy or thoracoabdominal access for safe resection. In patients who already had a prior contralateral adrenalectomy, partial adrenalectomy may be an option to preserve cortex and avoid hypocortisolism.

Despite preoperative α-blockade, patients may have either arrhythmias or hemodynamic instability during adrenalectomy. Some compensatory hypotension often results after the adrenal vein is ligated. Typically, this drop in blood pressure is minimized when blood volume is restored appropriately. Sometimes, intravenous boluses of crystalloid or colloid and pressor support are required to maintain blood pressure after resection.

While many patients with pheochromocytoma are hyperglycemic before resection, because of chronic catecholamine excess, they may be profoundly hypoglycemic in the early postoperative period (38). Frequent blood sugar checks are required in the early postoperative period to monitor for dangerous hypoglycemia, which may require a glucose drip.
Patients may continue to have high blood pressures after ressection due to underlying essential hypertension. Disease may recur in the contralateral adrenal gland or metastases years after surgery. Reoperative resection is the treatment of choice when complete extirpation is feasible. Furthermore, palliative debulking is often desirable in patients with disease that cannot be completely resected, as it can improve symptoms and the effectiveness of medical therapy.

**Pheochromocytoma Crisis**

Pheochromocytoma crisis is an uncommon event that requires prompt diagnosis and emergent medical intervention. The clinical presentation of pheochromocytoma crisis includes multisystem organ failure, fever (often >40°C), encephalopathy, and hemodynamic instability (9). A common error is the misdiagnosis of sepsis in patients whose condition continues to decline despite empiric antibiotic therapy.

Episodes of pheochromocytoma crisis are typically precipitated by traumatic stress, which is often iatrogenic. Furthermore, crises usually develop in undiagnosed or untreated patients without α-blockade. Patients in pheochromocytoma crisis should be transferred urgently to an intensive care unit, or to the highest level of care available.

Phentolamine, an intravenous α-blocker, should be given in 2 mg boluses. Larger doses can result in hypotension. Phenoxybenzamine and prazosin can also be used, but can be more difficult to titrate.

β-Blockade, without α-blockade, can precipitate hemodynamic instability, as unopposed α-stimulation can cause peripheral vasoconstriction (39). However, after initial α-blockade is started, β-blockade can effectively control heart rate and blood pressure.

Other useful medications include nitrates, such as sodium nitroprusside and nitroglycerine. These agents result in prompt venodilation, which can decrease cardiac preload and cause an immediate decline in blood pressure. Side effects from sodium nitroprusside include cyanide accumulation after long-term use. Ultimately, these agents should be used as adjuvant therapies after α-adrenergic blockade is achieved.

Ideally, real-time arterial pressure should be monitored with the placement of a radial artery arterial line. Measurement of urinary output with a bladder catheter is simple, quick, and useful. Central venous monitoring is not an essential component in the initial care of patients in pheochromocytoma crisis, and central venous catheter placement should not delay pharmacologic treatment. However, many pharmacologic agents require central venous delivery and central venous catheters are useful for monitoring volume status especially in patients with heart failure.

Emergent adrenalectomy should be avoided in patients during pheochromocytoma crisis (40). After the patient is stabilized and α-blockade instituted, planning should begin for elective adrenalectomy with curative intent. This can be performed during the same admission after preoperative planning, including the completion of localization studies and maximal tolerated doses of α-blockade. Although many experienced clinicians believe that 14 days of α-blockade are required, good outcomes have been reported with shorter preparation times.

**Pregnancy and Pheochromocytoma**

The stress of pregnancy and labor can prompt pheochromocytoma crisis and elicit symptoms in patients with unrecognized pheochromocytoma (41). On rare occasions, symptoms are minimal during gestation and manifest only after delivery (42). Obstetric outcomes are exceptionally poor when maternal pheochromocytoma is unrecognized; fetal and maternal mortality rates exceed 50% in such cases (43). However, others have reported favorable results when the diagnosis is established and the mother is adequately treated antenatally (44). While the presenting symptoms and the biochemical workup are no different in obstetric patients, maternal hypertension is often erroneously attributed to preeclampsia or eclampsia. Because of the grave consequences related to this missed diagnosis, pheochromocytoma should be considered in any hypertensive gravid woman.

The localization of pheochromocytoma lesions in pregnant women should avoid fetal exposure to ionizing radiation. Instead of CT and MIBG scanning, ultrasound and MRI can be used to avoid fetal exposure to ionizing radiation. Both α- and β-blockades can be given safely in the obstetric patient. The timing of surgical resection should be carefully planned. Usually adrenalectomy can be deferred until after planned cesarean section. If the diagnosis is made early in the gestational period and medical therapy is poorly tolerated, elective laparoscopic resection may also be safely performed during the second trimester. Surgery in the first trimester is associated with fetal loss and resection in the third trimester can be technically challenging because of the larger uterus, and can cause premature labor.

**CONCLUSION**

The diagnosis of pheochromocytoma should be considered in any patient with episodic symptoms, a family history of pheochromocytoma, hypertension at a young age, a known adrenal mass, hemodynamic instability in response to anesthesia, or refractory hypertension. The diagnosis is confirmed by elevated plasma free metanephrines or urinary fractionated metanephrines, which are typically elevated at least threefold. Pheochromocytoma crisis is a medical emergency that is often misdiagnosed as severe sepsis. Clinical outcomes are uniformly fatal when pheochromocytoma crisis is unrecognized. The initial therapy includes α-blockade titrated to orthostatic hypotension with salt loading. Both β-blockade and intravenous nitrates are useful adjuvant therapies to control tachycardia and hypertension, respectively. Ultimately, curative outcomes depend on complete surgical resection, which is most safely performed after optimization with α-blockade and saline resuscitation.

**Key Points**

- The Endocrine Society recently published practice guidelines for the evaluation and management of pheochromocytoma/paraganglioma (45).
- The diagnosis of pheochromocytoma should be considered in patients with severe hypertension, episodic symptoms, a family history of pheochromocytoma, hypertension at a young age, idiopathic dilated cardiomyopathy, known adrenal mass, hemodynamic instability during routine anesthesia, or refractory hypertension.
- Plasma free metanephrines or urinary fractionated metanephrines are the initial laboratory studies to rule out pheochromocytoma.
• α-Blockade with either phenoxycbenzamine or doxazosin should be started as soon as the biochemical diagnosis of pheochromocytoma is established.

• Preoperative salt loading and saline resuscitation should be used to minimize the orthostatic hypotension associated with α-blockade.

• After adequate α-blockade is established, β-blockers can be used as an adjuvant means of controlling tachycardia.

• Pheochromocytoma crisis is a medical emergency requiring immediate α-blockade and invasive hemodynamic monitoring; additional pharmacologic agents, such as β-blockers, calcium channel blockers, and intravenous nitrates, are often needed to control heart rate and blood pressure.

• The only curative therapy for pheochromocytoma is surgical resection; however, this should only be attempted on an elective basis after the patient is optimized for surgery with α-blockade and salt loading.

References


