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Pheochromocytoma and Paraganglioma Treatment (PDQ®)–Health Professional Version

Go to Patient Version

General Information About Pheochromocytoma and Paraganglioma

Pheochromocytomas and extra-adrenal paragangliomas are rare tumors arising from neural crest tissue that develops into sympathetic and parasympathetic paraganglia throughout the body.

The most recent World Health Organization classification utilizes the term *pheochromocytoma* exclusively for tumors arising from the adrenal medulla, and the term *extra-adrenal paraganglioma* for similar tumors that arise from other locations.[1]

Incidence and Mortality

The incidence of pheochromocytoma is 2 to 8 per million persons per year.[2,3] Pheochromocytoma is present in 0.1% to 1% of patients with hypertension,[4-6] and it is present in approximately 5% of patients with incidentally discovered adrenal masses.[7] The peak incidence occurs in the third to fifth decades of life; the average age at diagnosis is 24.9 years in hereditary cases and 43.9 years in sporadic cases.[8] The incidence is equal between males and females.[9]

Anatomy

Pheochromocytomas and extra-adrenal paragangliomas arise from neural crest tissue. Neural crest tissue develops into sympathetic and parasympathetic paraganglia.

Sympathetic paraganglia include the following:

- The adrenal medulla.
- The organ of Zuckerkandl near the aortic bifurcation.
- Other paraganglia along the distribution of the sympathetic nervous system.

Parasympathetic paraganglia include the following:

- The carotid body.
- Other paraganglia along the cervical and thoracic branches of the vagus and glossopharyngeal nerves.

Risk Factors

No known environmental, dietary, or lifestyle risk factors have been linked to the development of pheochromocytoma.

Hereditary Predisposition Syndromes

Of all pheochromocytomas and extra-adrenal paragangliomas, 25% occur in the setting of a hereditary syndrome.[8-10] Major genetic syndromes that have been identified as carrying an increased risk of pheochromocytoma are included in Table 1.

Table 1. Major Genetic Syndromes That Carry an Increased Risk of Pheochromocytoma

Genetic Syndrome or Condition	Affected Gene	Comment
Multiple endocrine neoplasia type 2A and 2B	*RET*	(Refer to the Pheochromocytoma section in the PDQ summary on the Genetics of Endocrine and Neuroendocrine Neoplasias for more information.)
von Hippel-Lindau disease	*VHL*	
Neurofibromatosis type 1	*NF1*	
Hereditary Paraganglioma Syndrome	*SDHD* [11]	Formerly referred to as familial pheochromocytoma-paraganglioma syndrome type 1
	SDHAF2 (*SDH5*) [12]	Formerly referred to as familial pheochromocytoma-paraganglioma syndrome type 2
	SDHC [13]	Formerly referred to as

Genetic Syndrome or Condition	Affected Gene	Comment
		familial pheochromocytoma-paraganglioma syndrome type 3
	SDHB [14]	Formerly referred to as familial pheochromocytoma-paraganglioma syndrome type 4
	SDHA [15]	

Pheochromocytomas and extra-adrenal paragangliomas can also occur in the following two other very rare syndromes:

- The Carney triad of extra-adrenal paraganglioma, gastrointestinal stromal tumor (GIST),[16] and pulmonary chondroma.
- The Carney-Stratakis dyad of paraganglioma and GIST.[17]

Other genetic causes of pheochromocytoma and paraganglioma are being studied. For example, truncating germline mutations in the transmembrane-encoding gene *TMEM127* on chromosome 2q11 have been shown to be present in approximately 30% of affected patients with familial disease and in about 3% of patients with apparently sporadic pheochromocytomas without a known genetic cause.[18] *TMEM127* is a negative regulator of mammalian target of rapamycin (mTOR) effector proteins.

Genetic counseling and testing

It has been proposed that all patients diagnosed with a pheochromocytoma or paraganglioma should consider genetic testing because the incidence of a hereditary syndrome in apparently sporadic cases is as high as 25%.[8,9,19] Early identification of a hereditary syndrome allows for early screening for other associated tumors and identification of family members who are at risk. In addition, some patients with a hereditary syndrome are more likely to develop multifocal, malignant, or recurrent disease. Knowledge of the specific genetic mutation permits increased vigilance during preoperative localization or postoperative surveillance of such patients.

Certain subgroups of patients are at very low risk of having an inherited syndrome (e.g., <2% in patients diagnosed with apparently sporadic pheochromocytoma after age 50 years).[8] Therefore, genetic testing for all patients diagnosed with a pheochromocytoma or

paraganglioma may not be practical or cost effective from a population standpoint. It is currently recommended that every patient diagnosed with a pheochromocytoma or extra-adrenal paraganglioma should first undergo risk evaluation for a hereditary syndrome by a certified genetic counselor. (Refer to the NCI Cancer Genetics Services Directory for a list of genetic healthcare professionals.)

Genetic testing is often recommended in the following situations:

- Patients with a personal or family history of clinical features suggestive of a hereditary pheochromocytoma-paraganglioma syndrome.
- Patients with bilateral or multifocal tumors.
- Patients with sympathetic or malignant extra-adrenal paragangliomas.
- Patients diagnosed before age 40 years.

In patients with a unilateral pheochromocytoma and no personal or family history suggestive of hereditary disease, genetic testing can be considered if patients are between the ages of 40 years and 50 years, but genetic testing is generally not recommended if patients are older than 50 years. If a mutation is identified, predictive genetic testing should be offered to asymptomatic at-risk family members. (Refer to the PDQ summary on the Genetics of Endocrine and Neuroendocrine Neoplasias for more information.)

Clinical Features

Patients with pheochromocytomas and sympathetic extra-adrenal paragangliomas may present with symptoms of excess catecholamine production, including the following:

- Hypertension.
- Headache.
- Perspiration.
- Forceful palpitations.
- Tremor.
- Facial pallor.

These symptoms are often paroxysmal, although sustained hypertension between paroxysmal episodes occurs in 50% to 60% of patients with pheochromocytoma.[20] Episodes of hypertension can be variable in frequency, severity, and duration and are often extremely difficult to manage medically. Hypertensive crisis can lead to cardiac arrhythmias, myocardial infarction, and even death.

Patients are often very symptomatic from excess catecholamine secretion. Symptoms of catecholamine excess can be spontaneous or induced by a variety of events, including the following:

- Strenuous physical exertion.

- Trauma.
- Labor and delivery.
- Anesthesia induction.
- Surgery or other invasive procedures, including direct instrumentation of the tumor (e.g., fine-needle aspiration).
- Foods high in tyramine (e.g., red wine, chocolate, and cheese).
- Urination (e.g., bladder wall tumor, which is rare).

Phenoxybenzamine (blocks alpha receptors) is an effective treatment for catecholamine excess and metyrosine (blocks catecholamine synthesis) can be added if needed.

Parasympathetic extra-adrenal paragangliomas do not secrete catecholamines and usually present as a neck mass with symptoms related to compression or are incidentally discovered on an imaging study performed for an unrelated reason. In addition, approximately half of patients with pheochromocytoma are asymptomatic because their neoplasms are discovered in the presymptomatic state by either abdominal imaging for other reasons (e.g., adrenal incidentalomas) or genetic testing in at-risk family members.[21-24]

Diagnostics

The diagnosis of pheochromocytoma is usually suspected by the presence of an adrenal mass or a workup. Biochemical testing is done to document excess catecholamine secretion. Once the biochemical diagnosis of a catecholamine-secreting tumor is confirmed, localization studies should be performed. Controversy exists as to the optimal single test to make the diagnosis.

Biochemical testing

24-hour urine collection

A 24-hour urine collection for catecholamines (e.g., epinephrine, norepinephrine, and dopamine) and fractionated metanephrines (e.g., metanephrine and normetanephrine) has a relatively low sensitivity (77%–90%) but a high specificity (98%). Pretest probability is also important. The specificity of plasma-free fractionated metanephrines is 82% in patients tested for sporadic pheochromocytoma versus 96% in patients tested for hereditary pheochromocytoma.[25,26]

Plasma-free fractionated metanephrines

Measurement of plasma-free fractionated metanephrines appears to be an ideal case-detection test for patients at higher baseline risk of pheochromocytoma. Examples of these patients might include the following:

- Patients with an incidentally discovered adrenal mass.
- Patients with a family history of pheochromocytoma.
- Patients with a known inherited predisposition to pheochromocytoma.

The test is associated with a relatively high false-positive rate in patients with a lower baseline risk of pheochromocytoma. Measurement of plasma-free metanephrines (e.g., metanephrine and normetanephrine) has a high sensitivity (97%–99%) but a relatively low specificity (85%).

In general, it is reasonable to use measurement of plasma-free fractionated metanephrines for initial case detection, which is followed by 24-hour measurement of urine-fractionated metanephrines and catecholamines for confirmation. Test results can be difficult to interpret because of the possibility of false-positive results. False-positive results can be caused by any of the following:[20,25]

- Common medications (e.g., tricyclic antidepressants).
- Physical or emotional stress.
- Inappropriately low reference ranges based on normal laboratory data rather than clinical data sets.[27]
- Common foods (e.g., caffeine and bananas) that interfere with specific assays and medications.

A mildly elevated catecholamine or metanephrine level is usually the result of assay interference caused by drugs or other factors. Patients with symptomatic pheochromocytoma almost always have increases in catecholamines or metanephrines two to three times higher than the upper limits of reference ranges.[20]

Provocative testing (e.g., using glucagon) can be dangerous, adds no value to other current testing methods, and is not recommended.[28]

Imaging studies

Computed tomography (CT) imaging or magnetic resonance imaging (MRI) of the abdomen and pelvis (at least through the level of the aortic bifurcation) are the most commonly used methods for localization.[29] Both have similar sensitivities (90%–100%) and specificities (70%–80%).[29] CT imaging provides superior anatomic detail compared with MRI.

Additional functional imaging may be necessary if CT imaging or MRI fails to localize the tumor. It might also be useful in patients who are at risk for multifocal, malignant, or recurrent disease. ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy coupled with CT imaging provides anatomic and functional information with good sensitivity (80%–90%) and specificity (95%–100%).[29] ^{131}I-MIBG can be used in the same way, but the image quality is not as high as with ^{123}I-MIBG.[30] Other functional imaging alternatives include ^{111}In-octreotide scintigraphy and ^{18}F-fluorodeoxyglucose positron emission tomography, both of which can be coupled with CT imaging for improved anatomic detail.

It is rare for localization of a catecholamine-secreting tumor to be unsuccessful if currently available imaging methods are used.

Prognosis and Survival

There are no clear data regarding the survival of patients with localized (apparently benign) disease or regional disease. Although patients with localized (apparently benign) disease should experience an overall survival approaching that of age-matched disease-free individuals, 6.5% to 16.5% of these patients will develop a recurrence, usually 5 to 15 years after initial surgery.[31-33]

Approximately 50% of patients with recurrent disease experience distant metastasis.[33] The 5-year survival in the setting of metastatic disease (whether identified at the time of initial diagnosis or identified postoperatively as recurrent disease) is 40% to 45%.[34]

Follow-up Evaluation

Long-term follow-up is essential for all patients with pheochromocytoma or extra-adrenal paraganglioma, even when initial pathology demonstrates no findings that are concerning for malignancy.[6]

- After resection of a solitary sporadic pheochromocytoma, patients should undergo baseline postoperative biochemical testing followed by annual lifelong biochemical testing.
- Patients who have undergone resection of a noncatecholamine-producing tumor should initially undergo annual imaging with computed tomography imaging or magnetic resonance imaging and periodic imaging with radiolabeled metaiodobenzylguanidine to monitor for recurrence or metastasis.
- Patients who have undergone resection of a pheochromocytoma or paraganglioma in the setting of a hereditary syndrome require lifelong annual biochemical screening in addition to routine screening for other component tumors of their specific syndrome.[6]

Related Summaries

Another PDQ summary containing information about pheochromocytoma and paraganglioma includes the following:

- Genetics of Endocrine and Neuroendocrine Neoplasias

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