Pheochromocytoma

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INTRODUCTION

Pheochromocytoma is a rare tumor of the adrenal gland. Most tumors occur sporadically, although about 10% occur as part of a hereditary syndrome such as von Hippel-Lindau disease, multiple endocrine neoplasia, or neurofibromatosis. Approximately 10% of pheochromocytomas are extra-adrenal, 10% are bilateral, and 10% are malignant. Extra-adrenal pheochromocytomas (also called paragangliomas) may arise from sympathetic ganglia anywhere in the body or from the organs of Zuckerkandl, the carotid body, or in the pelvis.

Pheochromocytoma is an uncommon but important cause of hypertension. In a study at the Cleveland Clinic, 4939 patients were evaluated from 1966 to 1967 for hypertension; 89% were found to have essential hypertension, and 9 patients (0.2%) were diagnosed with pheochromocytoma. Other studies have suggested a similar incidence of pheochromocytoma in the general population. In an analysis of Swedish National Cancer Registry data from 1958 to 1981, pheochromocytoma occurred at a rate of 2 cases per million population per year, with a slight preponderance (60% of cases) in women. A retrospective study of the population of Rochester, MN, from 1950 to 1979 estimated an average annual incidence of pheochromocytoma of 0.95 per 100,000 person-years, with 50% of the cases being discovered at autopsy and 76% of autopsy cases being unsuspected during life.

ADRENAL ANATOMY

Each of the paired normal adrenal glands weighs approximately 5 g. The 3 zones of the cortex surround the adrenal medulla, which is derived embryologically from the neural crest at about the seventh week of fetal development. The arterial blood supply (6 to 7 mL/g/min) for each adrenal gland is derived from branches of the renal artery, the aorta, and particularly the inferior phrenic arteries. Adrenal blood flow drains toward the medulla, where large venous sinusoids surround the chromaffin cells and facilitate the transport of catecholamines into the general circulation. These sinusoids form a single adrenal vein on each side, draining into the renal vein on the left side and directly into the inferior vena cava on the right side. The high concentrations of glucocorticoids draining into the medulla from the surrounding cortex may increase the production of the enzyme phenyl-ethanolamine-N-methyltransferase (PNMT). This enzyme, in turn, is responsible for the formation of epinephrine.

The epinephrine- and norepinephrine-secreting cells of the adrenal medulla are called chromaffin cells because they stain dark when exposed to chromium salts. These cells are arranged in nests, with abundant cytoplasm characterized by granules containing catecholamines, chromogranin, and other proteins. Microscopically, epinephrine- and norepinephrine-containing cells can be differentiated by the size of the granules (epinephrine granules are 190 nm in diameter and norepinephrine granules are 250 nm in diameter) and by differences in their electron density and membrane appearance.

CATECHOLAMINE PHYSIOLOGY

The basic unit for catecholamine synthesis is tyrosine, an amino acid that is hydroxylated to dopa (dihydroxyphenylalanine) by the enzyme tyrosine hydroxylase. This interaction is the rate-limiting step in catecholamine formation. Hydroxylation of tyrosine is increased by sympathetic nerve activity and decreased by higher intracytoplasmic levels of catecholamines.

Dopa is decarboxylated to dopamine, which is transported into cytoplasmic vesicles to be hydroxylated to norepinephrine by the enzyme dopamine β-hydroxylase. These steps are stimulated by glucocorticoids, and they occur in the adrenergic neurons of the sympathetic nervous system and also in the adrenal medullary chromaffin cells.

The enzyme PNMT, found primarily in the adrenal medulla, affects the N-methylation of norepinephrine to epinephrine. Thus, adrenergic nerve endings release only norepinephrine, whereas approximately 80% of the catecholamines released by the adrenal medulla are epinephrine. Epinephrine produces a feedback inhibition of PNMT activity. Although it is true that normal adrenal glands and small pheochromocytomas produce primarily epinephrine, larger pheochromocytomas may produce primarily norepinephrine, possibly because the amount
of glucocorticoids in the tumor is relatively lower and thus the degree of PNMT stimulation is lower as well.1

Catecholamines are released from their storage vesicles in response to sympathetic nerve stimulation produced by hypotension, pain, heat, cold, and other stressful conditions. In general, the sympathetic nerve endings and adrenal medulla release catecholamines in response to the same stimuli and the 2 systems support each other. However, adrenal catecholamine effects may last as much as 10 times longer than the effects of catecholamines released from sympathetic nerves. Most of the norepinephrine released from sympathetic nerve endings is quickly reabsorbed by the nerve endings (reuptake). The epinephrine released from the adrenal medulla by exocytosis is metabolized by 2 enzyme systems, which takes more time. The first of these enzymes is catechol-O-methyltransferase (COMT), found primarily in the liver and kidneys. COMT converts epinephrine and norepinephrine into metanephrine and normetanephrine, respectively.10 The second major enzyme is monoamine oxidase.11 The COMT and monoamine oxidase systems are responsible for the breakdown of catecholamines to vanillylmandelic acid (VMA) and homovanillic acid, the major products excreted in the urine.12

Catecholamines have effects throughout the organ systems of the body, mediated through adrenergic receptor types \( \alpha_1, \alpha_2, \beta_1, \) and \( \beta_2 \), as noted in Table 1.

### SPORADIC PHEOCHROMOCYTOMA

#### CASE 1: PRESENTATION

A 51-year-old man presents to his internist for evaluation of palpitations.

Two years ago, the patient underwent a single-vessel coronary bypass graft, after which he had an episode of atrial fibrillation that was successfully treated by amiodarone and procaainamide. Since then, the patient has noted intermittent episodes of palpitations, irregular heartbeat, and elevated blood pressure as high as 210/120 mm Hg. He also has felt shaky and tremulous at times. These episodes are becoming more frequent and now occur up to 4 times a day and last for as long as 30 minutes. The patient had been previously evaluated in a cardiology clinic by Holter monitoring; no arrhythmia was noted.

Physical examination is generally unremarkable. The patient’s pulse is 74 bpm and blood pressure is 120/74 mm Hg. Thyroid and cardiovascular examinations are normal at this time.

Based on the patient’s constellation of symptoms (ie, palpitations, irregular heartbeat, elevated blood pressure, feelings of shakiness and tremor), the internist makes a presumptive diagnosis of pheochromocytoma.

- What are typical presenting signs and symptoms of pheochromocytoma?

#### CLINICAL FEATURES

The most common symptoms of pheochromocytoma are headache, sweating, and palpitations. In one analysis of 324 patients, the symptoms of headache, sweating, and palpitations occurred in 60%, 52%, and 49% of patients, respectively, whereas pallor, nausea, tremor, and anxiety all occurred in 30% or more of patients.13 Abdominal pain, chest pain, weakness, flushing, and dyspnea were less common symptoms. In another series of 54 patients, headache, sweating, and palpitations each occurred in approximately 60% of patients.2 These symptoms characteristically occur episodically, with occurrences ranging from about once per week to several times daily. The episodes may last from 10 minutes to 1 or 2 hours.

The principal physical sign of pheochromocytoma is hypertension, which is sustained in approximately 50% of cases, paroxysmal in 30% to 40% of cases, and absent in 10% to 20% of cases.14 The hypertension is attributed to the circulating catecholamines secreted by the tumor, but the level of blood pressure elevation does not always correlate with plasma catecholamine levels, possibly because of varying numbers and sensitivity of

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**Table 1. Functional Effects of Adrenergic Receptors**

<table>
<thead>
<tr>
<th>( \alpha_1 ) Receptors</th>
<th>( \alpha_2 ) Receptors</th>
<th>( \beta_1 ) Receptors</th>
<th>( \beta_2 ) Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular smooth muscle contraction</td>
<td>Intestinal smooth muscle relaxation</td>
<td>Increase of cardiac rate and force</td>
<td>Smooth muscle (bronchial, urinary, vascular) relaxation</td>
</tr>
<tr>
<td>Prostatic smooth muscle contraction</td>
<td>Inhibition of pancreatic insulin secretion</td>
<td>Stimulation of renin release</td>
<td>Increase of insulin secretion</td>
</tr>
<tr>
<td>Liver glycogenesis</td>
<td>Inhibition of renin release</td>
<td>Stimulation of lipolysis</td>
<td>Liver glycogenolysis</td>
</tr>
</tbody>
</table>
α-adrenergic receptors or production of other vasoactive peptides. As in essential hypertension, the elevated blood pressure in pheochromocytoma is caused by increased total peripheral resistance. The heart rate is invariably increased, and normal cardiac output is maintained by a decreased stroke volume as a result of depletion of intravascular volume.

Other physical signs of pheochromocytoma are cardiac arrhythmia, weight loss, retinopathy, myocardial infarction, and myocarditis. Hypertrophic and dilated cardiomyopathy are unusual manifestations, which may be reversible with treatment of the pheochromocytoma.

**Differential Diagnosis**

Table 2 lists conditions that are in the differential diagnosis of pheochromocytoma as well as precipitating factors. The clinician must be aware that pheochromocytoma is a very unusual condition and that not all hypertensive patients need to be investigated. The major indications of pheochromocytoma are the classic triad of episodic symptoms—headache, diaphoresis, and palpitations—in addition to labile or paroxysmal hypertension. Other indications are refractory hypertension, severe hypertension or hypotension during anesthesia or surgery, family history of pheochromocytoma or multiple endocrine neoplasia, and adrenal masses discovered incidentally on radiographic studies.

**CASE 1: LABORATORY STUDIES**

The internist orders 24-hour urine collection to measure catecholamine metabolite levels, all of which are elevated. The metanephrine level is 1053 mg/24 hr (normal range, adults: 35–278 mg/24 hr), the normetanephrine level is 1179 mg/24 hr (normal range, adults: 110–720 mg/24 hr), and VMA excretion is 9.2 mg/24 hr (normal range, adults: 0.7–6.8 mg/24 hr; mean, 3.5 mg/24 hr). Urinary aldosterone and cortisol levels are also evaluated and found to be normal.

**BIOCHEMICAL STUDIES**

**Urinary Studies**

The standard biochemical evaluation for suspected cases of pheochromocytoma is the 24-hour urine collection for free catecholamines (epinephrine and norepinephrine) and their metabolites (metanephrine, normetanephrine, and VMA). Unfortunately, the urine collection procedure is awkward for the patient and may yield false-negative results in a patient with episodic symptoms. In addition, false-positive results may occur as a result of overcollection of urine, and false-negative results may occur as a result of undercollection of urine. These problems can be partially compensated for by measuring the metanephrine-to-creatinine ratio in the urine. Data from the National Institutes of Health indicate that urinary fractionated metanephrine levels have a greater sensitivity than VMA excretion for detecting pheochromocytoma (Table 3). There is also clear evidence that urinary fractionated metanephrine measurements are superior to total metanephrine measurements, which perhaps should be abandoned, for detecting pheochromocytoma.

**Plasma Studies**

Plasma catecholamine and metanephrine measurements have become more easily available since the early 1990s and are particularly sensitive if collected during a symptomatic episode. However, it is also theoretically
possible that these test results may be normal if samples are collected at a time when the patient is asymptomatic. As plasma catecholamine and metanephrine measurements have become more popular, however, it has become clear that these tests are quite reliable. National Institutes of Health data indicate sensitivity of 99% and specificity of 89% for plasma free metanephrine levels and sensitivity of 84% and specificity of 81% for plasma catecholamine levels.19 Plasma free metanephrine levels, thus, appear to provide the best test for excluding or confirming pheochromocytoma. Plasma free normetanephrine levels less than 112 pg/mL and metanephrine levels less than 61 pg/mL in a patient with pheochromocytoma suspected on clinical grounds reliably exclude the tumor—we further tests are necessary.20 In contrast, most patients with pheochromocytoma have plasma normetanephrine levels greater than 400 pg/mL and metanephrine levels greater than 220 pg/mL. These tests exclude the need for other screening tests or follow-up evaluations when negative and confirm a definite need for imaging studies when positive so that the tumor can be localized.

For the most reliable results, plasma catecholamine and metanephrine measurements should be performed after an overnight fast. The patient should be supine for at least 15 minutes prior to drawing the sample, because plasma normetanephrine and norepinephrine have been shown to increase by 27% and 130%, respectively, after a change from the supine to the upright position.21 One disadvantage of tests for plasma free metanephrine levels is that they are not yet widely available because of laboratory technical difficulties. Also, the specificity is relatively low; however, the consequences of a false-negative result are certainly potentially lethal, and therefore the excellent sensitivity of the plasma free metanephrine measurement makes this the current test of choice.

Clonidine Suppression Test

In some patients with a clinical suspicion of pheochromocytoma, baseline catecholamine testing may be normal. Clonidine is an α2-adrenoreceptor agonist that suppresses the release of catecholamines from sympathetic nerve endings, but not from tumors. The blood is drawn before the oral administration of 300 µg of clonidine and again 3 hours after administration. A positive clonidine suppression test indicates the failure of suppression of catecholamine levels. This test has 97% sensitivity but only 67% specificity.22

Glucagon Stimulation Test

This test is performed in the morning after an over-

ight fast. Venous blood is drawn before an intravenous bolus of 1 mg of glucagon is administered and 2 minutes after administration. When plasma catecholamine levels are increased 3-fold after glucagon administration, the test result is positive. Sensitivity is 81% and specificity is 99%.22

If both the clonidine suppression test and the glucagon stimulation test results are negative, pheochromocytoma can be almost certainly excluded.

CASE 1: IMAGING STUDIES

The internist informs the patient that his symptoms combined with the results of his urinary studies are highly suggestive of pheochromocytoma. She refers the patient to a urologist, who orders magnetic resonance imaging (MRI) of the abdomen. The MRI demonstrates a right adrenal mass measuring 2.9 × 2.5 × 2.2 cm (Figure).

- Which imaging studies are recommended for visualizing pheochromocytoma? In what setting may another imaging modality be favored?

PRIMARY IMAGING STUDIES

Computed tomography (CT) and MRI are the principal methods of adrenal imaging. CT is highly sensitive but cannot distinguish among adrenal adenomas, carcinomas, metastases, myelolipomas, or pheochromocytomas. Compared with CT, MRI offers the following advantages for adrenal imaging: 1) it does not require contrast medium, 2) it does not use ionizing radiation and can therefore be used in pregnant women, and 3) it provides superior anatomic detail in relation to local vasculature. MRI also is superior to CT in evaluating for possible pheochromocytoma, which will appear hypointense on T1-weighted images and hyperintense on T2-weighted images. Abdominal ultrasonography may incidentally discover an adrenal mass but is not

Table 3. Sensitivity and Specificity of Urinary Tests for Pheochromocytoma

<table>
<thead>
<tr>
<th>Urinary Test</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
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</thead>
<tbody>
<tr>
<td>Fractionated metanephrines</td>
<td>97</td>
<td>69</td>
</tr>
<tr>
<td>Total metanephrines</td>
<td>77</td>
<td>93</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>86</td>
<td>88</td>
</tr>
<tr>
<td>Vanillylmandelic acid</td>
<td>64</td>
<td>95</td>
</tr>
</tbody>
</table>

indicated for investigation of a known adrenal tumor.

ADDITIONAL IMAGING STUDIES

Metaiodobenzylguanidine (MIBG) scintigraphy is useful in situations in which CT or MRI scans fail to localize a pheochromocytoma. In addition, MIBG scintigraphy is used to rule out metastatic disease. Scanning is performed at 48 and 72 hours after administration of MIBG. The sensitivity of MIBG scintigraphy is high but the specificity is low. $^{131}$I-MIBG is superior to $^{123}$I-MIBG; however, $^{123}$I-MIBG is not widely available and is difficult to work with because it has a half-life of only 13 hours. For these reasons, many institutions do not use MIBG scintigraphy.

Another modality infrequently used for imaging pheochromocytomas is octreotide scintigraphy. Octreotide is an analogue of somatostatin, which can be labeled with $^{125}$I or $^{111}$In-DTPA (diethylenetriamine pentaacetic acid). Octreotide binds to somatostatin receptors in endocrine pancreatic tumors, carcinoid tumors, and pheochromocytomas. The sensitivity of octreotide scans is low. Finally, positron emission tomography, which is currently in the investigational stages, appears to be superior to other nuclear imaging techniques for evaluation of both primary and metastatic pheochromocytomas.

CASE 1: SURGICAL MANAGEMENT

The urologist recommends adrenalectomy based on the following factors: presence of a definite adrenal mass on MRI, positive results on the patient’s biochemical studies, symptoms strongly supportive of pheochromocytoma, and no family history of pheochromocytoma or other endocrine or neurologic lesions that may indicate the possibility of multiple tumors or extra-adrenal lesions.

- What is the preoperative management for a patient with pheochromocytoma?
- What surgical approach is preferred?

PREOPERATIVE MANAGEMENT

$\alpha$-Adrenergic Plus $\beta$-Adrenergic Blockade

Pheochromocytoma-induced hypertension is caused by vasoconstriction and increased peripheral resistance, with relative hypovolemia. The traditional approach to management of the preoperative patient is to institute $\alpha$-blockade for hypertension control approximately 2 weeks before surgery. Phenoxybenzamine is the $\alpha$-blocker of choice because it is noncompetitive and therefore will not be overwhelmed during the operation by the large amount of catecholamines that may be released by pressure on the tumor. The typical starting dose is 10 mg twice daily; the dose is then increased by 10 mg/day until good blood pressure control is achieved, which may require 40 to 50 mg twice daily. Orthostatic hypotension, somnolence, headache, and nasal congestion may occur. An alternative to phenoxybenzamine is doxazosin 5 mg/day, a selective $\alpha_1$-adrenoreceptor inhibitor, which also promotes volume repletion by vasodilation.

Appropriate $\alpha$-blockade leads to a reflex tachycardia, which is controlled by adding a $\beta$-adrenergic blocking
agent. Labetalol, in doses up to 1600 mg/day, or propranolol, up to 40 mg 3 times daily, is used.\textsuperscript{27} α-blockade must always be started before β-blockade or hypertension may be worsened by unopposed vasoconstriction.

**Combined Medical Blockade**

Combined medical blockade is the combination of α- and β-blockade with metyrosine, which competitively inhibits tyrosine hydroxylase, the rate-limiting enzyme in catecholamine production. Administration of metyrosine for 2 weeks preoperatively decreases tumor catecholamine content by 50% to 80%.\textsuperscript{28} The dose is 250 mg every 6 hours for the first week followed by 500 mg every 2 days to maintain blockade in the second week. A dose of 1 g is administered at midnight before the day of surgery. Approximately 10% of patients taking metyrosine experience side effects, including depression, sleep disturbances, tremor, and sedation.

**INTRAOPERATIVE MANAGEMENT**

The operation should be performed by an experienced surgical and anesthesia team that communicates well. The initial procedure is the placement of an arterial line and 2 intravenous lines prior to induction of anesthesia. The objective of anesthetic management during surgery is to avoid excessive increases or decreases in blood pressure and to avoid cardiac arrhythmias. Anesthesia is induced with thiopental, followed by nitrous oxide and methoxyflurane, neither of which causes release of catecholamines. Significant blood pressure increases are managed with phentolamine and nitroprusside. Hypotension may require intravenous infusion of norepinephrine or epinephrine along with rapid fluid infusion. Glucose levels should be monitored when the tumor is removed because sudden hypoglycemia may occur.\textsuperscript{28}

**SURGICAL APPROACH**

Open surgical excision of the pheochromocytoma is the traditional operation. A transverse abdominal incision can be used for unilateral or, if bilateral tumors are present, for bilateral adrenalectomy. The open incision also allows abdominal exploration for extra-adrenal tumors. As imaging techniques have improved, however, the exact location, laterality, and singularity of the tumor can be determined with more certainty, and the flank incision has become the incision of choice for most cases.

Laparoscopy has recently proven to be equally effective for removal of pheochromocytomas, with most laparoscopic surgeons favoring the transperitoneal approach.\textsuperscript{29} Laparoscopic surgery for pheochromocytoma appears to be similar to laparoscopic removal of other adrenal tumors in terms of operative difficulty, operative time, amount of blood loss, rate of complications, and conversion rate to open surgery (1% to 5% of cases).\textsuperscript{29} As with open surgery, early ligation of the adrenal vein is important, and the adrenal gland is manipulated as little as possible. Large tumor size does not appear to hinder the laparoscopic approach; tumors up to 15 cm have been removed, sometimes with hand-assistance.\textsuperscript{29} Laparoscopic partial adrenalectomies have been reported in patients with bilateral and familial tumors and have been successful in preserving sufficient cortical tissue to avoid the need for steroid replacement therapy.\textsuperscript{30,31}

Operative time for laparoscopy is equivalent to open surgery, and the intraoperative incidence of hypertensive or hypotensive episodes is no greater than that during open surgery. Advantages of the laparoscopic approach compared with open surgery include less blood loss, shorter length of hospital stay, and shorter recovery time. As is true for any surgical procedure, the laparoscopic approach has a learning curve. In one series, this rate was approximately 25 cases, with decreased operative time and blood loss as experience increased; in addition, the size of lesions managed surgically increased as surgical expertise increased.\textsuperscript{29}

**POSTOPERATIVE FOLLOW-UP**

In the immediate recovery period, repletion of intravascular volume may be necessary as the effects of α-blockade wear off. The half-life of phenoxybenzamine is 24 hours, and the half-life of metyrosine is 4 hours.\textsuperscript{28} Hypoglycemia may occur postoperatively. Recovery should be rapid following laparoscopic surgery, with discharge from the hospital in about 3 days. Catecholamine levels should return to normal approximately 2 weeks after surgery; evaluation of catecholamine levels after 6 weeks is recommended. Elevations at this stage may indicate persistent, multifocal, or metastatic tumor, and further investigations will be necessary. Approximately 20% to 30% of patients may have persistent postoperative hypertension, which is usually essential hypertension.\textsuperscript{33} All patients who undergo surgical treatment of pheochromocytoma should have annual evaluation by biochemical screening, because the recurrence rate is approximately 2% to 5% at 10 years for sporadic pheochromocytoma.\textsuperscript{34,35}

**CASE 1: OUTCOME**

Two weeks after combined medical blockade, the patient undergoes an uneventful laparoscopic adrenalectomy. The pathology report confirms a pheochromocytoma. Following the surgery, the patient’s symptoms resolve and his blood pressure normalizes.
catecholamine evaluations are normal. Five years after the operation, the patient remains healthy, with normal blood pressure and no recurrence of symptoms.

**FAMILIAL PHEOCHROMOCYTOMA**

**VON HIPPEL-LINDAU DISEASE**

Von Hippel-Lindau (VHL) disease is an inherited autosomal dominant tumor syndrome characterized by a germline mutation in the VHL gene, a tumor suppressor gene located at chromosome 3p25. Four VHL gene subtypes are described (Table 4). VHL germline mutations are observed in 100% of families with more than one affected member. The great majority are missense mutations.

The incidence of VHL disease is 1 in 36,000 live births. Patients are predisposed to retinal or cerebellar and spinal hemangioblastomas; clear cell renal carcinomas; pheochromocytomas; pancreatic islet cell tumors; and cysts and adenomas in the kidneys, pancreas, and epididymis. The primary cause of death in these patients is renal cell carcinoma with metastases or cerebellar hemangioblastoma. In patients with VHL disease, the lifetime risk of developing hemangioblastoma or renal cell cancer is estimated at 70%, whereas the risk of pheochromocytoma is estimated at 14%. Individuals with VHL gene subtypes 1 and 2B have an average life expectancy of 60 years, whereas individuals with VHL gene subtypes 2A and 2C have normal life expectancy.

**Clinical Features and Findings**

Approximately 20% to 50% of patients with pheochromocytoma-associated VHL disease have hypertension, and approximately 20% to 50% of these patients are symptomatic. The incidence of signs and symptoms increases with tumor size.

In one series of 30 patients with VHL disease and pheochromocytoma, 7 were hypertensive (only 1 patient had paroxysmal hypertension), and 10 were symptomatic (8 patients had headache, 6 had sweating and palpitations). Tumor tissue analysis of pheochromocytomas from these patients revealed that 98% of the catecholamine level was norepinephrine and normetanephrine.

The patient’s past surgical history also includes right and left partial nephrectomies for renal cell carcinoma, 3 spinal operations for hemangioblastoma, a cerebellar operation for hemangioblastoma, and laser surgery to remove bilateral retinal angiomas. The patient is paraplegic and legally blind as a result of her health problems. At today’s visit, she mentions that she has had some recent episodes of sweating and palpitations that she believes are caused by menopause.

The patient is referred to a urologist for MRI, which reveals a right adrenal mass 2.5 cm in diameter and 2 left renal masses that are suspicious for cystic renal cell carcinoma.

- Are the signs and symptoms of pheochromocytoma in VHL disease the same as those in sporadic pheochromocytoma? Is catecholamine production similar in both types of pheochromocytoma?
- How is the diagnosis of VHL disease made?

### Table 4. von Hippel-Lindau (VHL) Gene Subtypes and Associated Lesions

<table>
<thead>
<tr>
<th>VHL Gene Subtype</th>
<th>Associated Lesions</th>
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<tbody>
<tr>
<td></td>
<td>Retinal Hemangioblastoma</td>
</tr>
<tr>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td>2A</td>
<td>+</td>
</tr>
<tr>
<td>2B</td>
<td>+</td>
</tr>
<tr>
<td>2C</td>
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the tumors. In another series, 13 of 37 (35%) patients with known VHL disease were totally asymptomatic and found to have pheochromocytoma on urinary screening. The relatively high percentage of asymptomatic patients may be a result of screening studies in these patients, which resulted in early discovery of pheochromocytomas when the tumors are still small and catecholamine production is relatively low.

Screening and Diagnosis

DNA analysis is the most reliable method to screen for and diagnose VHL disease. Screening should be recommended for patients with family members who have VHL disease and for patients with multiple VHL-associated tumors, multiple pheochromocytomas, bilateral tumors, early-onset renal cell carcinomas, or hemangioblastomas. Tumors discovered by screening studies may be followed safely if the patient is asymptomatic. Doubling time of such tumors appears to be 17 months.

Case 2: Surgical Management and Outcome

The patient undergoes right adrenalectomy by open surgical technique. The surgeon chooses this approach versus laparoscopic adrenal surgery because the patient previously underwent right renal surgery, which may potentially complicate the laparoscopic approach to adrenalectomy. A left nephrectomy is performed during the same operative time. The patient recovers well and takes steroid replacement therapy. She has no further renal or pheochromocytoma complications.

- What other syndromes are associated with familial pheochromocytoma?
- Do germline mutations occur in sporadic pheochromocytoma?

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

Multiple endocrine neoplasia type 2 (MEN-2) is an autosomal dominant syndrome of variable penetrance characterized by medullary carcinoma of the thyroid (MCT) or hyperplasia of the thyroid C cells. Children of affected individuals have a 35% chance of developing the syndrome. The gene responsible is the RET proto-oncogene at chromosome 10q11. The incidence of MEN-2 is approximately 1 in 30,000 births. The mean age at diagnosis is 38 years, versus 47 years in sporadic cases. There are 3 subtypes of MEN-2. MEN-2A is characterized by MCT in virtually all patients, pheochromocytoma in approximately 50% of patients, and parathyroid hyperplasia or adenoma in approximately 35% of patients. MEN-2B is characterized by one or more of the following: MCT, pheochromocytoma, marfanoid habitus, mucosal neuromas, ganglioneuromas of the gastrointestinal tract, and, occasionally, hyperparathyroidism. Patients with the third subtype of MEN-2 have familial medullary thyroid carcinoma.

Pheochromocytomas are bilateral in 83% of cases of MEN-2. The tumors primarily produce epinephrine, associated with overexpression of PNMT. These tumors are more likely to be symptomatic than those associated with VHL disease. Of patients with MEN-2, 40% have hypertension and 60% are symptomatic.

DNA testing in families with MEN-2 identifies individuals with the mutation. Those without the mutation do not require any further screening or treatment, and those with the mutation should undergo annual testing for thyroid disease and pheochromocytoma as early as age 3 to 5 years, with thyroidectomy or adrenalectomy if indicated.

NEUROFIBROMATOSIS TYPE 1

Neurofibromatosis (NF) is characterized by café au lait spots, neurofibromas, hamartoma of the iris, and scoliosis. NF is divided into 2 subtypes: NF1 and NF2. NF1 accounts for 90% of cases and is also called von Recklinghausen’s disease. NF1 is inherited as an autosomal dominant condition, which occurs in 1 of 3000 live births. The NF1 gene is a tumor-suppressing gene localized to chromosome 17q11.2.

A literature review from 1999 reveals that pheochromocytoma was found in 0.1% to 5.7% of patients with NF1. Of these patients, 148 cases of pheochromocytoma were diagnosed (124 unilateral, 14 bilateral, and the remainder ectopic). Hypertension was present in 61% of patients with NF1 and pheochromocytoma, and all of these patients were symptomatic. Of the 148 cases of pheochromocytoma, 17 patients had malignant tumors and 15 had metastases at presentation.

SUCCINATE DEHYDROGENASE MUTATIONS

Mutations in the genes for succinate dehydrogenase (SDH) subunit B and SDH subunit D are occasionally associated with pheochromocytoma. These mutations may occur in sporadic or familial cases.

MUTATIONS IN SPORADIC TUMORS

Germline mutations are also found in nonfamilial pheochromocytoma. One study suggests that less than 10% of sporadic cases have mutations in the RET gene and less than 8% have mutations in the VHL gene. Another study found that 66 of 271 nonsyndromic cases of pheochromocytoma had mutations in the genes VHL, RET, SDH subunit B, or SDH subunit D. Interestingly, these patients presented at a mean age of 24.9 years as
compared with 43.9 years for patients without mutations. Also, patients with mutations had a much higher incidence of multifocal and extra-adrenal lesions.

MALIGNANT PHEOCHROMOCYTOMA

Approximately 10% of pheochromocytomas are malignant. There may be a female preponderance. Malignancy in pheochromocytoma is diagnosed by tumor behavior rather than histologic appearance. The diagnostic criteria are invasion of adjacent tissue or lymph nodes and metastatic disease, either concurrent or recurrent postoperatively.

The main therapeutic modality is surgical excision of the primary tumor and metastatic areas to the greatest extent possible. Associated hypertension and symptoms of residual metastatic disease can be well managed by α- and β-blockade when necessary.

Chemotherapy for malignant pheochromocytoma using cyclophosphamide, vincristine, and dacarbazine has been described. Of 14 patients who were treated, 2 had a complete clinical response and 5 had a partial response (judged by disappearance of all or more than 50% of clinical or radiologic evidence of disease). In addition, complete and partial biochemical responses were achieved in 3 and 8 patients, respectively. The response duration averaged 21 months.

As noted previously, 131I-MIBG scintigraphy is a potentially useful diagnostic modality for pheochromocytoma. 131I-MIBG is also used as a therapeutic modality in malignant and metastatic disease. The prescribed dose is 100 to 200 mCi, and multiple doses may be given to deliver more than 5000 cGy to a tumor. A literature review revealed that complete response rates (defined as radiologic disappearance of tumor) of 5% have been observed, with partial response rates (reduction of the tumor by more than 50%) of 26% and 18% reported. Biochemical responses were noted in approximately 40% of patients. Further, the review found that soft tissues responded better than bone. Relapse was common within a median of 19 months: of initial responders, 33% died at a median of 22 months; of nonresponders, 45% died at a median of 14 months.

SPECIAL POPULATIONS

PHEOCHROMOCYTOMA IN PREGNANCY

Pheochromocytoma during pregnancy is highly unusual, and the diagnosis is made prepartum in only approximately one third of cases. Maternal and fetal mortality rates are both approximately 50%—a rate that is considerably reduced by early diagnosis and appropriate management.

Patients may present with severe eclampsia or the typical paroxysmal hypertension associated with sweating, anxiety, and palpitations. Biochemical evaluation for pheochromocytoma in pregnant patients is the same as previously described (24-hour urine collection for free catecholamines and their metabolites as well as the clonidine suppression test and glucagon stimulation test). MRI scanning can be performed safely because this modality does not use ionizing radiation.

Prazosin is used for α-blockade rather than phenoxybenzamine because of possible mutagenic effects associated with the latter drug. Before 24 weeks of pregnancy, surgical removal of the tumor is advised. After week 24, medical management is initiated; a Caesarean section followed by immediate removal of the pheochromocytoma can be performed at term. Laparoscopic removal has been described in 2 pregnant patients at 16 and 20 weeks.

PHEOCHROMOCYTOMA IN CHILDREN

The prevalence of hypertension in children is about 2%, and pheochromocytoma is responsible for 1% of these cases. Approximately 30% of these cases of pheochromocytoma are extra-adrenal. The typical age of onset in children is 8 or 9 years. Approximately 10% of cases of pheochromocytoma in children are familial.

Symptoms in children are similar to those in adults, although the hypertension in children is usually sustained rather than paroxysmal. Children who have a family history of VHL or MEN-2 disease should undergo biochemical screening annually. MRI and/or MIBG scanning can be performed in children if pheochromocytoma is suspected.

Surgical excision is usually successful, and the laparoscopic approach is increasingly used. Annual postoperative follow-up should be performed for 15 years.

REFERENCES

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