Pheochromocytoma: current diagnosis and management

WILLIAM M. MANGER, MD, PhD, AND RAY W. GIFFORD, Jr, MD

BACKGROUND  Pheochromocytoma is a catecholamine-secreting tumor of chromaffin cells that causes hypertension.

OBJECTIVE  To review the clinical presentation, diagnosis, and treatment of this disease.

SUMMARY  Pheochromocytoma can mimic a number of other diseases, making recognition difficult. Hypertension may be paroxysmal or sustained. The signs and symptoms of pheochromocytoma are mostly due to hypercatecholaminemia, hypertension, complications, or coexisting diseases; however, measurements of catecholamines and their metabolites in the plasma and urine may be normal between "attacks", and other conditions can elevate these values. The clonidine suppression test confers specificity to the clinical and laboratory findings, and magnetic resonance imaging is the most reliable method of locating a tumor. Surgical resection is successful in 90% of patients; however, the disease is fatal if it is not detected and treated.

CONCLUSIONS  Pheochromocytoma should be suspected in patients with paroxysmal or sustained hypertension, particularly if symptoms are present.

INDEX TERMS: PHEOCHROMOCYTOMA; HYPERTENSION
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FOR THE CLINICIAN, pheochromocytoma is a most fascinating and exciting tumor; for the patient, this pharmacologic bomb poses great risk of death or devastating complications. Pheochromocytoma can be totally removed in 90% of patients who have it, but it will likely prove fatal if unrecognized. The deceptive and treacherous nature of this rare tumor is underscored by the Mayo Clinic experience: of 54 patients who were found to have pheochromocytomas at autopsy, tumors were not suspected in 75% and contributed to death in 55%

With current diagnostic modalities, the presence of a pheochromocytoma can almost always be established or rejected; however, the secret of improved recognition of this endocrine tumor rests on a high index of suspicion. It is crucial to think of pheochromocytoma in all patients with sustained or paroxysmal hypertension—especially those who are symptomatic.

CLINICAL PRESENTATION

Because it secretes catecholamines, often episodically, pheochro-
Table 1

Symptoms reported by 76 patients (almost all adults) with pheochromocytoma associated with paroxysmal or persistent hypertension*

<table>
<thead>
<tr>
<th>Symptoms presumably due to excessive catecholamines or hypertension</th>
<th>Paroxysmal (37 patients) %†</th>
<th>Persistent (39 patients) %†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches (severe)</td>
<td>92</td>
<td>72</td>
</tr>
<tr>
<td>Excessive sweating (generalized)</td>
<td>65</td>
<td>69</td>
</tr>
<tr>
<td>Palpitations with or without tachycardia</td>
<td>73</td>
<td>51</td>
</tr>
<tr>
<td>Anxiety, nervousness, fear of impending death, or panic</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td>Tremulousness</td>
<td>51</td>
<td>26</td>
</tr>
<tr>
<td>Pain in chest, abdomen (usually epigastric), lumbar regions, lower abdomen or groin</td>
<td>48</td>
<td>28</td>
</tr>
<tr>
<td>Nausea with or without vomiting</td>
<td>43</td>
<td>26</td>
</tr>
<tr>
<td>Weakness, fatigue, prostration</td>
<td>38</td>
<td>15</td>
</tr>
<tr>
<td>Weight loss (severe)</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Warmth or heat intolerance</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Dizziness or faintness</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Constipation (or rarely diarrhea)</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Paresthesia or pain in arms</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Bradycardia (noted by patient)</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Grand mal seizures</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

Miscellaneous (A large number of miscellaneous symptoms have been reported. Especially noteworthy are painless hematuria, frequency, nocturia, and tenesmus in pheochromocytoma of the urinary bladder)

Manifestations due to complications

- Congestive heart failure with or without cardiomyopathy
- Myocardial infarction
- Cerebrovascular accident
- Ischemic enterocolitis with or without megacolon
- Azotemia
- Dissecting aneurysm
- Enccephalopathy
- Shock
- Hemorrhagic necrosis in a pheochromocytoma

Manifestations due to coexisting diseases or syndromes

- Cholelithiasis
- Medullary thyroid carcinoma with or without effects of secretions of serotonin, calcitonin, prostaglandin, or adrenocorticotropic hormone-like substance
- Hyperparathyroidism
- Mucocutaneous neuromas with characteristic facies
- Thickened corneal nerves (seen only with slit lamp)
- Marfanoid habitus
- Alimentary tract ganglioneuromatosis
- Neurofibromatosis and its complications
- Cushing’s syndrome (rare)
- Von Hippel-Lindau disease (rare)
- Virilism, Addison’s disease, acromegaly, duodenal carcinoid (extremely rare)

Symptoms caused by encroachment on adjacent structures or by invasion and pressure effects of metastases

*From Manger and Gifford, reference 4.
†Approximate percent.

Pheochromocytoma frequently presents dramatically and explosively with numerous and diverse manifestations that mimic many diseases. Of great diagnostic importance is the presence of sustained or paroxysmal hypertension. Manifestations or “attacks” suggesting hypercatecholaminemia without hypertension are highly atypical. Rarely, hypertension will be absent; this is most common when pheochromocytoma is familial.

One or more symptomatic attacks occur weekly in 75% of patients; however, attacks may occur several times daily or only every few months. Attacks occur abruptly and subside slowly: they last less than 1 hour in 80% of patients, but they may last less than a minute or persist for a week. They may be precipitated by palpation of the tumor, postural changes, exertion, anxiety, trauma, pain, ingestion of foods or beverages containing tyramine (certain cheeses, beers, and wines) or synephrine (citrus fruit), use of certain drugs (histamine, glucagon, tyramine, phenothiazine, metoclopramide, adrenocorticotropic hormone), intubation, anesthesia, operative manipulation, and micturition or bladder distension (with bladder tumors).

The symptoms and signs of pheochromocytoma (Tables 1 and 2) are mainly due to hypercatecholaminemia, hypertension, complications, or coexisting diseases or syndromes.

Headaches occur in any part of the head; they may be mild but are usually severe and throbbing (especially during paroxysmal hypertension) and are often accompanied by nausea and vomiting.

Generalized sweating (sometimes drenching) and palpitations with tachycardia (or reflex bradycardia)...
occur frequently. Acute anxiety with fear of death is
often experienced.

Hypermetabolism may cause considerable weight
loss, but some patients, especially those with parox-
ysmal hypertension, may remain obese. Severe con-
striction or pseudo-obstruction may occur in pa-
tients with sustained hypertension because catecholamines inhibit peristalsis. Ischemic enterocolitis with intestinal necrosis may complicate in-
tense mesenteric artery vasoconstriction caused by hypercatecholaminemia. Secretion of vasoactive in-
testinal peptide, serotonin, or calcitonin by some pheochromocytomas may cause diarrhea. Severe wa-
ter diarrhea may be accompanied by hypokalemia
and hypochlorhydria or achlorhydria (Verner-Morri-
son WDHH or WDHA syndrome). Marked systolic
and diastolic hypertension usually occurs with paro-
xysmal attacks, which occur in 45% of patients; rarely,
paroxysms will convert to sustained hypertension.
With sustained hypertension, which occurs in 50%
of patients, blood pressures may fluctuate widely, and
paroxysms may result from variations in circulating
catecholamines. The remainder of patients have lit-	tle hypertension, if any. Very rarely, hypertension
alters with hypotension (with predominantly epinephrine-secreting tumors).

About 5% of patients remain normotensive, es-
specially those with familial pheochromocytoma.
Patterns of hypertension in familial disease remain
consistent (ie, family members have either sustained
or paroxysmal hypertension). Very rarely, a rapid
progression in severity and frequency of hyperten-
sive attacks (sometimes alternating with hypoten-
sion) may necessitate emergency surgery to remove
the tumor.

No close correlation exists between blood pres-
sure and plasma catecholamine concentrations; the
sympathetic nervous system contributes to mainte-
nance of hypertension in clinical as well as experi-
mental pheochromocytoma.

Orthostatic hypotension in untreated hyperten-
sive patients suggests pheochromocytoma. When
this occurs, blood pressure usually decreases to nor-
motensive levels; rarely, the blood pressure falls to
shock levels and is accompanied by tachycardia.
Resistance to antihypertensive therapy, paradoxic
blood pressure increases during treatment with beta
blockers, guanethidine, or ganglionic blockers, or
marked pressor responses to conditions mentioned
above that may precipitate attacks should suggest
pheochromocytoma.

Pallor and tachycardia (or reflex bradycardia) fre-
quently occur, and, rarely, flushing is observed dur-
ing hypertensive paroxysms. Retinopathy is not in-
frequent when hypertension is severe and sustained,
but it rarely occurs when hypertension is paroxys-
mal. Occasionally, a fine tremor and Raynaud's phe-
nomenon are noted. Slight temperature elevation is
common and severe hyperpyrexia may rarely occur.

In children, polydipsia, polyuria, and convulsions
may also occur, and, rarely, the hands become puffy,
red, and cyanotic. Attacks of pheochromocytoma
may be aggravated or may subside during pregnancy.

### TABLE 2

<table>
<thead>
<tr>
<th>SIGNS OBSERVED IN PATIENTS WITH PHEOCHROMOCYTOMA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure changes</td>
</tr>
<tr>
<td>Hypertension with or without wide fluctuations</td>
</tr>
<tr>
<td>(rarely paroxysmal hypertension or hypertension</td>
</tr>
<tr>
<td>alternating with hypotension, or hypertension</td>
</tr>
<tr>
<td>absent.)</td>
</tr>
<tr>
<td>Hypertension induced by physical maneuver such</td>
</tr>
<tr>
<td>as exercise, postural change, or palpation and</td>
</tr>
<tr>
<td>massage of flank or mass elsewhere</td>
</tr>
<tr>
<td>Orthostatic hypertension with or without postural</td>
</tr>
<tr>
<td>tachycardia</td>
</tr>
<tr>
<td>Paradoxic blood pressure response to certain</td>
</tr>
<tr>
<td>antihypertensive drugs; marked pressor response</td>
</tr>
<tr>
<td>with induction of anesthesia</td>
</tr>
<tr>
<td>Other signs of catecholamine excess</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
</tr>
<tr>
<td>Tachycardia or reflex bradycardia, very forceful</td>
</tr>
<tr>
<td>heartbeat, arrhythmia</td>
</tr>
</tbody>
</table>
| Pallor of face and upper part of body (rarely fl-
| ushing; mottled cyanosis)                        |
| Anxious, frightened, troubled appearance         |
| Hypertensive retinopathy                         |
| Dilated pupils (very rarely exophthalmos, lacri-
| mation, scleral pallor, or injection; pupils may|
| not react to light)                              |
| Leanness or underweight                         |
| Tremor with or without shaking                   |
| Raynaud's phenomenon or livedo reticularis (occa-
| sionally puffy, red, and cyanotic hands in chil-
| dren); skin of extremities wet, cold, clammy, pa-
| le, gooseflesh; occasionally cyanotic nail beds  |
| Fever (occasionally very elevated)               |
| Mass lesion (rarely palpable)                    |
| Tumor in abdomen or neck (pheochromocytoma, chemo-
| dectoma, thyroid carcinoma, or thyroid-swelling  |
| (very rare and only during hypertensive paroxysm)| |
| Signs caused by encroachment on adjacent struc-
| tures or by invasion and pressure effects of tech-
| asures                                    |
| Manifestations related to complications or to co-
| existing diseases or syndromes†                  |

*Observed in some of the 76 patients cited in Table 1.

†See Table 1.
PHEOCHROMOCYTOMA • MANGER AND GIFFORD

FIGURE 1. Lesions of the lips, tongue, and corneas observed in four patients with multiple endocrine neoplasia, type 3.

(A) Diffuse thickening of the lower lip in a patient with medullary thyroid carcinoma (MTC) and pheochromocytoma. Thickening of upper lip is less prominent but is irregular and accentuated centrally (arrow) and produces a bumpy appearance.

(B) Multiple sessile confluent nodules stud tip of tongue in a patient with MTC without evidence of pheochromocytoma. Slightly elevated plaque-like lesions, more evident on right (arrow) are present along margins of tongue.


(D) Thickened corneal nerve of right and left eyes and thickened perilimbal neuromas are visible on either side of each limbus (arrows). (Drawing from Robertson DM, Sizemore GW, Gordon H. Thickened corneal nerves as a manifestation of multiple endocrine neoplasia. Trans Am Acad Ophthalmol Otolaryngol 1975; 5:733.)

and can be confused with eclampsia; shock may occur with labor or after delivery and may mimic a ruptured uterus. Tumors in the bladder may cause painless hematuria, and attacks may occur during micturition or bladder distension.

ASSOCIATED ENTITIES

Ten percent of pheochromocytomas are familial as indicated by their occurrence in families and by their coexistence with multiple endocrine neoplasia (MEN). Coexistence with medullary thyroid carcinoma (MTC) or C-cell hyperplasia and sometimes parathyroid neoplasms or hyperplasia constitutes MEN type 2. Coexistence of pheochromocytoma, MTC, mucosal neuromas, thickened corneal nerves, alimentary tract ganglioneuromatosis, and, often, a marfanoid habitus constitutes MEN type 3 (Figure I). Hyperparathyroidism occurs in 50% of patients with MEN type 2 but rarely in MEN type 3.

MTC involves both thyroid lobes and frequently spreads to cervical and mediastinal nodes. Serotonin, prostaglandin, and calcitonin may be released from MTC and may cause severe diarrhea; adrenocorticotropic hormone-like substances may be secreted by MTCs or pheochromocytomas and can cause Cush- ing’s syndrome. Patients with pheochromocytoma should be screened for
MTC or premalignant C-cell hyperplasia and hyperparathyroidism. MTC may occur years before pheochromocytoma.4,7 Hypercalcitoninemia suggests MTC or C-cell hyperplasia; however, hypercalcitoninemia occurs in other conditions and occasionally in pheochromocytoma.4,7 Similarly, hypercalcemia may not indicate MEN, since it may result from a parathyroid-like hormone released from some pheochromocytomas.10 Therefore, reevaluation for MEN should be performed after removal of a pheochromocytoma.

Neurofibromatosis (Von Recklinghausen’s disease), often with “café-au-lait” spots, occurs in 5% of patients with pheochromocytoma, whereas the incidence of pheochromocytoma in neurofibromatosis is 1%. Coexistence of neurofibromatosis, pheochromocytoma, and somatostatin-rich duodenal carcinoid was reported in one patient.11 Rarely, pheochromocytoma coexists with von Hippel-Lindau disease (cerebellar hemangioblastoma plus retinal angioma) or acromegally. The high incidence of cholelithiasis (up to 30%) in patients with pheochromocytoma remains unexplained.

APUD is an acronym indicating cells having similar cytochemical behavior (ie, they produce amines by amine precursor uptake and decarboxyla-

### TABLE 3

**DIFFERENTIAL DIAGNOSIS OF PHEOCHROMOCYTOMA**

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>All hypertensive patients (sustained and paroxysmal) when cause is unknown</td>
</tr>
<tr>
<td>Anxiety, panic attacks, psychoneurosis, tension states</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Paroxysmal tachycardia</td>
</tr>
<tr>
<td>Hyperdynamic beta-adrenergic circulatory state</td>
</tr>
<tr>
<td>Menopause</td>
</tr>
<tr>
<td>Vasodilating headache (migraine and cluster headaches)</td>
</tr>
<tr>
<td>Coronary insufficiency syndrome</td>
</tr>
<tr>
<td>Acute hypertensive encephalopathy</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Renal parenchymal or renal arterial disease with hypertension</td>
</tr>
<tr>
<td>Focal arterial insufficiency of the brain; cerebral vasculitis</td>
</tr>
<tr>
<td>Intracranial lesions (with or without increased intracranial pressure)</td>
</tr>
<tr>
<td>Autonomic hyperreflexia</td>
</tr>
<tr>
<td>Diencephalic seizure; Page’s syndrome; dopamine surges</td>
</tr>
<tr>
<td>Toxemia of pregnancy (or eclampsia with convulsions)</td>
</tr>
<tr>
<td>Hypertensive crises associated with monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>Carcinoid</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Mastocytosis</td>
</tr>
<tr>
<td>Familial dysautonomia</td>
</tr>
<tr>
<td>Acrodynia</td>
</tr>
<tr>
<td>Neuroblastoma; ganglioneuroblastoma; ganglioneuroma</td>
</tr>
<tr>
<td>Acute infectious disease; acute abdomen (cardiovascular catastrophe)</td>
</tr>
<tr>
<td>Unexplained shock</td>
</tr>
<tr>
<td>Neurofibromatosis (with or without renal arterial disease)</td>
</tr>
<tr>
<td>Fatal familial insomnia</td>
</tr>
<tr>
<td>Rare causes of paroxysmal hypertension (adrenal medullary hyperplasia; acute porphyria; lead poisoning; tabetic crisis; encephalitis; clonidine withdrawal; hypovolemia with inappropriate vasoconstriction; pulmonary artery; fibrosarcoma; pork hypersensitivity; dysregulation of hypothalamus; baroreflex failure; tetanus; Guillain-Barré syndrome; pseudopheochromocytoma: factitious-induced by certain illegal, prescription and nonprescription drugs)</td>
</tr>
<tr>
<td>Fortuitous circumstances simulating pheochromocytoma</td>
</tr>
<tr>
<td>Conditions sometimes associated with pheochromocytoma</td>
</tr>
<tr>
<td>Coexisting disease or syndromes</td>
</tr>
<tr>
<td>Cholelithiasis</td>
</tr>
<tr>
<td>Medullary thyroid carcinoma</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Mucosal neuromas</td>
</tr>
<tr>
<td>Thickened corneal nerves</td>
</tr>
<tr>
<td>Marfanoid habitus</td>
</tr>
<tr>
<td>Alimentary-tract ganglioneuromatosis</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Von Hippel-Lindau disease</td>
</tr>
<tr>
<td>Polycythemia</td>
</tr>
<tr>
<td>Virilism, Addison's disease, acromegaly</td>
</tr>
<tr>
<td>Complications</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Renovascular disease</td>
</tr>
<tr>
<td>Circulatory shock</td>
</tr>
<tr>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Hemorrhagic necrosis of pheochromocytoma</td>
</tr>
<tr>
<td>Ischemic enterocolitis with or without intestinal obstruction</td>
</tr>
</tbody>
</table>

*Conditions in italics may have increased excretion of catecholamines and/or metabolites from Manger and Gifford, reference 4 with modification.*

†May present as an abdominal or cardiovascular catastrophe.
TABLE 4

INDICATIONS FOR SCREENING PATIENTS FOR PHEOCHROMOCYTOMA*

Hypertension (sustained or paroxysmal) with the following:
- Symptoms (Table 1) and signs (Table 2) or coexisting disease or syndromes (Table 3)
- Group 3 or 4 retinopathy of unknown cause
- Weight loss
- Hyperglycemia
- Hypermetabolism without hyperthyroidism
- Cardiomyopathy
- Resistance to antihypertensive therapy
- Orthostatic hypotension (without antihypertensive drugs)
- Unexplained fever
- Persons with marked hyperlability of blood pressure
- Recurrent attacks of symptoms and signs of pheochromocytoma even if hypertension not demonstrated
- Severe pressor response during or induced by the following:
  - Anesthesia induction
  - Intubation
  - Surgery
  - Angiography
  - Parturition
  - Antihypertensive therapy
  - Precipitating factors listed under "Clinical Presentation" in text
- Unexplained circulatory shock – especially:
  - During anesthesia
  - During pregnancy, delivery, or in puerperium
  - During operation or postoperatively
  - Following administration of phenothiazine drugs
- Family history of pheochromocytoma, especially if hypertensive (also screen siblings and children)
- Hypertension with disease or complications sometimes associated with pheochromocytoma (Table 1)
- Hyperlabile blood pressure or severe hypertension during pregnancy or apparent preeclampsia or eclampsia
- Transient abnormal electrocardiogram during hypertensive episodes
- Imaging evidence of suprarenal mass


DIFFERENTIAL DIAGNOSIS

Many conditions can produce manifestations suggesting pheochromocytoma (Table 3). Most of these conditions can be excluded on clinical grounds, and most of these are discussed in detail elsewhere. Preoperative diagnosis of pheochromocytoma requires demonstration of substantial elevations of catecholamines or their metabolites in plasma or urine. Neural crest tumors, increased intracranial pressure, hypoglycemia, convulsions, clonidine withdrawal, baroreflex failure, surreptitious catecholamine administration, or consumption of certain illegal and prescription drugs may also cause substantial elevations of these substances, but few conditions increase them to levels occurring with pheochromocytoma. Physicians should be aware that many types of stress can significantly elevate these concentrations as well.

Consumption of certain controlled and illegal substances (amphetamine, cocaine, phencyclidine [PCP], lysergic acid diethylamide [LSD]) and of some prescription and nonprescription drugs containing phenylpropanolamine may cause manifestations mimicking pheochromocytoma. Factitious manifestations in emotionally disturbed persons who have access to prescription and illicit drugs should be considered in the differential diagnosis. Hemorrhagic necrosis in a pheochromocytoma may present as an acute abdomen or cardiovascular catastrophe.

DIAGNOSIS

Since 95% of patients are symptomatic, all patients with sustained or paroxysmal hypertension who have manifestations suggesting pheochromocytoma should be screened, unless the cause of hypertension is known. Asymptomatic patients with hypertension of unknown cause should be screened if they have laboratory or electrocardiographic abnormalities caused by hypercatecholaminemia, radiographic or magnetic resonance imaging (MRI) evidence suggesting pheochromocytoma, or diseases sometimes coexisting with pheochromocytoma (Table 1). Other indications for screening are listed in Table 4. Screening should be performed by measuring 24-hour urinary metanephrine excretion or plasma catecholamine concentrations. Urinary catecholamine and vanillylmandelic acid measurements are less reliable.
TABLE 5
PHEOCHROMOCYTOMA “PEARLS” (FACTS WORTH MEMORIZING)*

| 6 Hs‡ | Hypertension
|       | Headache
|       | Hyperhidrosis
|       | Heart consciousness
|       | Hypermetabolism
|       | Hyperglycemia
| 95% will have | Headache or hyperhidrosis or palpitation
| Rough rule of 10 | 10% familial
|            | 10% bilateral (adrenal)‡
|            | 10% malignant
|            | 10% multiple (other than bilateral adrenal)‡
|            | 10% extra-adrenal
|            | 10% occur in children
| Multiple endocrine neoplasm syndrome, type-2 triad | Medullary thyroid carcinoma
|            | Bilateral-familial pheochromocytoma (frequent)
| Multiple endocrine neoplasm syndrome, type-3 sextet | Bilateral-familial pheochromocytoma (frequent)
|            | Mucosal neuromas
|            | Thickened corneal nerves
|            | Marfanoid habitus
|            | Alimentary tract ganglioneuromatosis (very rarely hyperparathyroidism)
| 4 Cs | Cholelithiasis
|       | Cushing’s syndrome (very rare)
|       | Cutaneous lesions
|       | Cerebellar hemangioblastoma (very rare)

Manifestations may appear during pregnancy!

*Adapted from Manger and Gifford, reference 4.
†The term “triad of Hs” was used by Dr. John E. Howard and refers to hypertension, hyperglycemia, and hypermetabolism (without hyperthyroidism) occurring in patients with pheochromocytoma. We have extended this category to include 6 Hs.
‡Adults and children combined.

Unrecognized pheochromocytoma in pregnancy carries a high risk of maternal and fetal mortality. Manifestations may first appear in pregnancy, remit after delivery, and return in a subsequent pregnancy. Table 5 contains facts helpful in evaluating patients for pheochromocytoma.

Laboratory and electrocardiographic abnormalities

Laboratory abnormalities sometimes caused by pheochromocytoma and coexisting conditions are enumerated in Table 6 and are reviewed elsewhere.‡ Hyperglycemia, hypermetabolism, increased free fatty acid concentrations, and hypercholesterolemia may result from hypercatecholaminemia. Hypovolemia occurs in the majority of patients, primarily those with sustained hypertension. Rarely, pheochromocytomas (or an associated cerebellar hemangioblastoma) secrete erythropoietin and cause polycythemia.

TABLE 6
LABORATORY FINDINGS SOMETIMES PRESENT IN PHEOCHROMOCYTOMA*

| Fasting hyperglycemia (two thirds of patients with sustained hypertension) |
| Glycosuria |
| Impaired glucose tolerance |
| Increased basal metabolic rate (>20%) (three fourths of sustained hypertensive patients) |
| Increased plasma free fatty acid concentrations (mainly in sustained hypertensive patients) |
| Increased triglycerides |
| Hypercholesterolemia |
| Anemia or polycythemia; increased white blood cell count; usually erythrocyte sedimentation rate normal (occasionally increased platelet count) |
| Decreased plasma or total blood volume, or both |
| Increased blood urea but rare (<60 mg/dL in 95%); with or without proteinuria (rarely slight increase in serum creatinine) |
| Hyperreninemia with or without aldosteronism |
| Hypokalemia |
| Increased serum glucagon concentration |
| Hypercalcemia (caused by pheochromocytoma) |
| Hypoinsulinemia (rarely hyperinsulinemia and hypoglycemia) |
| Hyperamylasemia |
| Lactic acidosis (decreased pH, decreased PO₂, increased phosphorus) |
| Increased serum PTH-like substance, adrenocorticotropic hormone, vasoactive intestinal peptide, calcitonin, serotonin, gastrin, opioids, melanocyte-stimulating hormone, atrial natriuretic peptide, somatostatin (all rarely elaborated by pheochromocytoma) |

If associated with:

Cushing’s syndrome
- Increased serum adrenocorticotropic hormone (from pheochromocytoma or medullary thyroid carcinoma)
- Increased plasma cortisol
- Increased urinary steroids
Hyperparathyroidism
- Increased serum calcium
- Increased serum parathyroid hormone
- Decreased serum phosphate
Medullary thyroid carcinoma
- Increased serum thyrocalcitonin
- Increased serum prostaglandin (E₂ and F₂α)
- Increased serum serotonin
- Increased urinary 5-hydroxyindoleacetic acid
- Increased serum histaminase
- Increased adrenocorticotropic hormone concentration

*Modified from Manger and Gifford, reference 4.
Severe catecholamine-induced ischemia involving multiple organs may result in lactic acidosis and elevations of pancreatic, hepatic, and cardiac enzymes. Hypertension may be exacerbated by elevated plasma concentrations of renin, angiotensin II, and aldosterone resulting from catecholamine stimulation of renal beta-adrenergic receptors or, rarely, from renal artery spasm or compression by a pheochromocytoma or coexisting neurofibroma.

Arrhythmias or electrocardiographic changes suggesting myocardial ischemia, damage, or strain may develop; although nonspecific, their transient appearance during paroxysms suggests pheochromocytoma in the absence of other causes. Permanent electrocardiographic changes can result from hypertension, coronary atherosclerosis, or catecholamine cardiomyopathy. Catecholamine cardiomyopathy may occur in patients with sustained or only paroxysmal hypertension or, rarely, with normotension.

Biochemical tests
Concentrations of plasma catecholamines and excretion of urinary metanephrines are invariably elevated when pheochromocytoma causes sustained hypertension; when hypertension is only paroxysmal, measurements of catecholamines and their metabolites in plasma and urine may be normal during normotensive periods. If hypertension is paroxysmal, one must obtain blood during spontaneous or provoked hypertension or collect urine following a hypertensive episode to establish the preoperative diagnosis.

Pharmacologic tests
Some patients with essential or neurogenic hypertension have borderline or moderate elevations of plasma or urinary catecholamines or their metabolites (plasma catecholamine concentrations may be 500 to 2000 pg/mL under basal conditions). Often, these patients even have manifestations suggesting pheochromocytoma.

Diagnostic specificity is conferred by suppressing the sympathetic nervous system with clonidine; this reduces plasma norepinephrine by 50% or to normal concentrations in neurogenic hypertensive patients, but not in patients with pheochromocytoma.

Changes in the plasma epinephrine concentration are a less reliable diagnostic guide; rarely, significant increases in epinephrine consistent with pheochromocytoma have been observed during clonidine suppression. The test is quite safe, although clonidine’s vagotonic effect can cause marked hypotension, particularly in the presence of beta blockade; patients should remain recumbent until this drug effect subsides. Beta blockers should be discontinued 48 hours before testing since they can prevent significant suppression of plasma catecholamine concentrations by clonidine in patients with normotensive
genic hypertension and falsely suggest the presence of a pheochromocytoma. A few drugs (eg, isoproterenol, methyldopa, levodopa) cause significant spurious elevations of plasma catecholamine concentrations determined radioenzymatically; however, a variety of drugs may interfere with high-pressure liquid chromatographic catecholamine assays (Table 7). A catecholamine assay of blood drawn via an indwelling catheter from a patient who has been recumbent for 1 hour usually differentiates neurogenic from pheochromocytic hypertension; the clonidine suppression test is reserved for patients whose catecholamine concentrations remain elevated despite 1-hour recumbency.

Elevated catecholamine concentrations in platelets and decreased numbers of beta-adrenoceptors on leukocytes have been reported in pheochromocytic, but not neurogenic, hypertension.

Rarely, a provocative test with glucagon combined with plasma catecholamine measurement is required to establish the presence of a paroxysmally secreting pheochromocytoma. Testing is safe when performed with precautions to counteract hypertensive crises, arrhythmias, or hypotension; it is contraindicated when blood pressure is greater than 160/105 mm Hg or if sudden pressure elevations may be hazardous. Creating an alpha-adrenergic blockade or administering 10 mg of nifedipine orally prior to testing prevents a hypertensive response without influencing a diagnostic plasma catecholamine elevation.

Measurement of 24-hour urinary total metanephrines (metanephrine plus normetanephrine) is a highly reliable screening test, since these are elevated in about 95% of patients with pheochromocytoma.

Table 7 gives upper limits for normal excretion of catecholamines and their metabolites and indicates substances that can affect their determinations. We are unaware of drugs (except for metyrosine) that lower excretion of catecholamines or metabolites to normal levels in patients with pheochromocytoma; however, radiopaque media containing methylglucamine can cause false-negative results for metanephrines.

**PREOPERATIVE LOCALIZATION**

Pheochromocytomas arise from chromaffin cells in the adrenal medulla (90% of tumors), the organ of Zuckerkandl and other extra-adrenal sites in the abdomen, chest (< 2% of tumors), and neck (< 0.1% of
tumors), and in such exotic sites as the base of the skull, middle ear, and spermatic cord. Multiple and extra-adrenal pheochromocytomas are more common in children (35%) than adults (8%). If a significant fraction of plasma or urinary catecholamines is epinephrine or its metabolite (metanephrine), the pheochromocytoma is probably in the adrenal area, or, rarely, in the organ of Zuckerkandl; however, imaging studies must establish tumor location.

**Imaging**

Computed tomography (CT) identifies 95% of pheochromocytomas and reveals adrenal lesions 1 cm or larger and extra-adrenal lesions 2 cm or larger. Intravenous and oral contrast media may be needed for optimal interpretation. CT is noninvasive and superior to angiography, which is now rarely indicated. It reliably demonstrates chest lesions, although intrapericardial pheochromocytomas may be missed. MRI is the most reliable method of locating a pheochromocytoma. A high signal intensity on MRI is characteristic of pheochromocytoma (Figure 2). Rarely, other benign or malignant lesions may mimic pheochromocytoma. MRI probably identifies more than 95% of tumors. It is noninvasive and does not produce artifacts like those caused by surgical clips in CT. It is superior to CT in detecting extra-adrenal lesions and some cardiac and familial adrenal pheochromocytomas.

The radiopharmaceutical agent metaiodobenzylguanidine I131 (MIBG) concentrates in 85% of pheochromocytomas, and MIBG scintigraphy is highly specific for diagnosing pheochromocytoma and locating tumors. It is especially helpful in detecting very small tumors, tumors in unusual locations (eg, in the pericardium), and, perhaps, adrenal medullary hyperplasia (experience of E.L. Bravo). MIBG uptake may occur in neuroblastoma, MTC, carcinoid, and small-cell carcinoma of the lung. Drugs such as labetalol, reserpine, calcium antagonists, tricyclic antidepressants, sympathomimetics, cocaine, adrenergic neuron blockers, and tranquilizers may inhibit uptake and should be discontinued a week before scintigraphy.

CT, MRI, and scintigraphy with MIBG may locate bladder pheochromocytomas, but cystoscopy should be performed only after alpha-adrenergic blockade. Experience locating pheochromocytomas in the neck and base of the skull is limited; however, MRI and MIBG scintigraphy may prove most reliable.

Because scintigraphy with MIBG produces images of the entire body, it is particularly valuable in detecting metastases. Scanning with technetium 99 may demonstrate bone metastases missed by MIBG. Liver metastases can be detected with MRI or CT. Metastases usually involve the lymph nodes, liver, lungs, and bones, but not the brain.

**Central venous blood sampling**

When all attempts to locate a pheochromocytoma have failed, blood sampling for catecholamine assay from various sites in the vena cava may locate an abdominal tumor or indicate a thoracic or cervical lesion.

The algorithm in Figure 3 can be followed if pheochromocytoma is suspected.

**PREOPERATIVE EVALUATION AND MANAGEMENT**

MTC, C-cell hyperplasia, and hyperparathyroidism must be excluded in all patients with pheochromocytoma and in relatives of patients with familial pheochromocytoma. Diagnosis and treatment of these conditions should be delayed until after the pheochromocytoma is removed.

Malignant hypertension, acute cardiovascular or abdominal complications (eg, hemorrhagic necrosis of a pheochromocytoma), or acceleration in the frequency and severity of hypertensive crises may necessitate immediate medical or surgical therapy, or both, but this does not often happen.

Hypertensive crises are usually aborted by a rapid intravenous bolus of phentolamine (5 mg); if there is no response, the dose can be repeated every 2 minutes until the blood pressure is adequately reduced. Since phentolamine's effect is transient, repeated hypertensive crises (eg, those during surgery) are best controlled by infusing sodium nitroprusside or phentolamine (100 mg of either drug in 500 mL 5% dextrose in water) at a rate that normalizes blood pressure. Nitroprusside can cause thiocyanate toxicity if the infusion is prolonged or if renal function is impaired. Blood pressure should be lowered cautiously to avoid myocardial ischemia.

If immediate surgery is needed, hypovolemia is corrected by infusion of appropriate intravenous fluids within 18 hours preoperatively to minimize postoperative hypotension.

Abdominal palpation and stressful procedures should be performed cautiously, and drugs should be
Suspicion of pheochromocytoma
Sporadic - 95% symptomatic;
Familial (multiple endocrine neoplasia type 2 or 3) -
sometimes asymptomatic
Measure 24-hour urine metanephrines (avoid strenuous exercise) or plasma catecholamines (at basal state)

Normal

Hypertensive Normotensive, but high clinical suspicion
Remeasure metanephrines and plasma catecholamines at time of spontaneous hypertension or just after provocative test

If minimal suspicion exists, normal total metanephrines can almost always exclude pheochromocytoma; if metanephrines, vanillylmandelic acid, and catecholamines are all normal, pheochromocytoma is definitely excluded
Discontinue search

If either is elevated (≥ 3 x upper limit of normal)
Remeasure metanephrines and perform clonidine suppression test
Magnetic resonance imaging (MRI) or computed tomographic (CT) scan of abdomen and pelvis (we believe MRI is superior); oblique chest roentgenogram

Tumor not located
MRI or CT scan of chest, neck, and head MIBG scintigram (if available) of entire body

Tumor not located
Vena cava sampling

Tumor not located
Cystoscopy

Explore abdomen and pelvis (after eliminating other causes of elevated plasma catecholamines)

Tumor located
If there is suspicion of metastatic or multiple pheochromocytoma, metaiodobenzylguanidine 1131 (MIBG) and Tc 99 bone scan should be performed preoperatively
Operate

Tumor not located
Tumor located and removed
Treat medically and reevaluate later

If either is elevated (> 3 x upper limit of normal)

available to combat hypertensive crises, hypotension, and arrhythmias. Morphine and phenothiazines should be avoided, since they may precipitate hypertensive crises or shock.

**Adrenergic blockade**

Preoperative alpha blockade with phenoxybenzamine (10 to 20 mg twice daily) or prazosin (starting with 1 mg and increasing to 1 or 2 mg two or three times daily) for a week or longer and continuing until surgery usually minimizes preoperative manifestations, reverses hypovolemia, and promotes smooth anesthetic induction and relatively stable blood pressure during surgery. However, blockade is optional unless patients have severe sustained or paroxysmal hypertension or cardiovascular complications. Moreover, the dosage should be kept low enough to avoid orthostatic hypotension because higher dosages would prevent the blood pressure elevation caused by intra-abdominal palpation (which aids the surgeon in locating tumors), and prevent recognition of additional pheochromocytomas (which, without blockade, cause persistence of hypertension after tumor removal).

Extensive experience at the Cleveland Clinic revealed that preoperative alpha-adrenergic blockade with phenoxybenzamine or large doses of prazosin was not essential for successful surgical management and a satisfactory outcome for patients with pheochromocytoma. Preoperative beta blockade (propranolol 10 to 40 mg two or three times daily), if not contraindicated, is used for hazardous supraventricular arrhythmias, tachycardia, or angina. To rapidly control tachycardia due to atrial fibrillation or flutter, intravenous esmolol (a rapid-acting cardioselective beta1-blocker) may be effective. Ventricular arrhythmias are treated with lidocaine (50 to 100 mg intravenous bolus). Beta blockers should never be given without first creating alpha blockade, since beta blockade used alone can cause marked hypertension. This occurs particularly with nonselective beta blockers (eg, propranolol, nadolol), since they inhibit the vasodilating effects of epinephrine. Cardioselective beta blockers (eg, metoprolol, atenolol) have less vascular effect and are more appropriate.

Labetalol (an alpha-beta blocker) is effective in treating some patients with pheochromocytomas; however, we prefer not to use it, since it sometimes causes hypertension.

**OPERATIVE AND POSTOPERATIVE MANAGEMENT**

In expert hands, operative mortality is low (0 to 4%). Preoperatively, a tranquilizer is given to allay anxiety, which could trigger catecholamine release. Fentanyl and droperidol may stimulate tumor catecholamine secretion and are to be avoided. We avoid atropine since it may induce tachycardia in the presence of hypercatecholaminemia. Before endotracheal intubation, muscle relaxants are administered and electrocardiographic and intra-arterial pressure monitoring is initiated. Isoflurane is the preferred anesthetic, although enflurane is suitable.

During intubation and surgery, it is critical to treat hypertensive crises promptly with intravenous phentolamine or nitroprusside and to control arrhythmias with intravenous propranolol (esmolol may be preferable) or lidocaine, or both. Intraoperative replacement of blood loss will prevent postoperative hypotension.

Since intra-abdominal tumors may be multiple and extra-adrenal, an anterior transperitoneal incision is mandatory. Intra-abdominal neurofibromatosis, vascular lesions, and cholelithiasis may require additional surgery. We avoid bilateral prophylactic adrenalectomy, although some authorities recommend it when an adrenal pheochromocytoma occurs in MEN syndromes; their rationale is the great likelihood that both adrenals are, or will become, involved.

Hypercalcitoninemia and hypercalcemia are reevaluated after the pheochromocytoma has been removed; return of serum calcium and calcitonin concentrations to normal levels rules out other endocrine neoplasms as their cause.

Pheochromocytomas of the head, neck, chest, and bladder require special surgical procedures; otherwise, management is similar to that for intra-abdominal tumors. Pheochromocytomas discovered during pregnancy should be removed when the diagnosis is made; however, if the pregnancy is carried to term, cesarean section is advisable to avoid the stress of labor.

Close postoperative monitoring is mandatory. Hypovolemia and hemorrhage at operative sites can cause hypotension and require volume replacement. Fluid overload, pain, hypoxia, hypercapnia, urinary retention, or residual pheochromocytoma can cause postoperative hypertension. Inadvertent renal artery ligation can cause hyperreninemia; however, hypertension would probably not appear for several
days or weeks postoperatively.

Severe hypoglycemia with central nervous system manifestations has occurred within 2 hours after surgery. It is a transient phenomenon caused by a rise in insulin levels; alpha blockers may augment it by reducing inhibition of insulin secretion by catecholamines. Beta blockers can impair recovery from hypoglycemia by reducing gluconeogenesis and glycogenolysis, and they mask hypoglycemic signs by preventing tachycardia and tremor; in some cases sweating may also be impaired. Blood glucose should be monitored for several hours postoperatively, and hypoglycemia should be treated promptly. Initiating an infusion of 5% dextrose and water immediately after tumor removal and continuing it for several hours prevents hypoglycemia. Transient hyperinsulinemia with hypoglycemia was reported following glucose tolerance tests in two patients with pheochromocytoma.

Why 25% of patients remain hypertensive following tumor removal is unclear; coexisting essential hypertension may be a partial explanation. Five-year survival with benign pheochromocytomas is 95% but varies from 36% to 50% with malignant tumors.

LONG-TERM MEDICAL MANAGEMENT

If a pheochromocytoma cannot be totally removed, as much as possible is resected to reduce the amount of catecholamine-secreting tissue.

Conventional radiotherapy of bone metastases may be effective. Irradiation with MIBG may cause tumor regression and may decrease catecholamine secretion in 25% of malignant pheochromocytomas; however, since all patients treated with MIBG relapsed within 2 years, this therapy has been curtailed in the United States.

Combination intravenous chemotherapy with cyclophosphamide, vincristine, and dacarbazine temporarily reduces tumor mass, catecholamine excretion, and symptoms in 50% of patients with malignant pheochromocytoma. Since damaged cells may release catecholamines, treatment of hypertensive crises is sometimes required during chemotherapy.

Alpha and beta blockers can control manifestations of hypercatecholaminemia for many years, and beta blockers may prevent catecholamine-induced cardiomyopathy. Metyrosine decreases catecholamine synthesis and minimizes manifestations of hypercatecholaminemia, and it appears useful in treating catecholamine-induced cardiomyopathy.

Nifedipine (10 mg orally) is especially effective in promptly resolving hypertensive crises. It can suppress clinical symptoms without altering plasma catecholamine concentrations, although a significant decrease in norepinephrine excretion occurred in one patient with pheochromocytoma.

Somatostatin can be useful in hypersecretory diarrhea. In one of our patients, large intravenous doses of somatostatin partially controlled severe secretory diarrhea caused by marked elevation of plasma vasoactive intestinal peptide and calcitonin concentrations.

SUMMARY

Pheochromocytoma can be difficult to recognize: the key to diagnosing it is suspecting it in patients with paroxysmal or sustained hypertension, especially those with any manifestations suggesting hypercatecholaminemia. Measurements of catecholamines and their metabolites in plasma or urine provide definitive information in about 95% of patients with pheochromocytoma, but the clonidine suppression test may be needed to rule out neurogenic hypertension. Rarely, a provocative test may be required to stimulate a quiescent tumor. MRI or CT imaging or scintigraphy with MIBG can be used to localize tumors, but MRI appears the most reliable. Management requires expertise; surgical resection is successful in 90% of patients.

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