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# CLINICAL REVIEW 164

# The Laboratory Diagnosis of Adrenal Pheochromocytoma: The Mayo Clinic Experience

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PHEOCHROMOCYTOMA, a catecholamine-producing tumor arising in the adrenal medulla, has an estimated incidence of two to eight cases per million persons annually (1, 2). Its clinical hallmark is sustained or intermittent hypertension often associated with paroxysmal symptoms (3). Pheochromocytoma should also be considered if a patient has labile hypertension, hypertension resistant to antihypertensive therapy, or paroxysmal symptoms ("spells") (3, 4). Correct diagnosis is important because resection of the tumor dramatically reverses the clinical symptoms and may cure the hypertension (5). A missed or delayed diagnosis may cause considerable morbidity and mortality (5, 6).

Clinically significant pheochromocytoma was first recognized in 1926 when Cesar Roux in Switzerland and Charles H. Mayo in the United States successfully removed pheochromocytomas to cure the catecholamine-associated symptom complex (7, 8). A biochemical assessment of catecholamine hypersecretion was not possible in 1926. Since then, the diagnostic approach has progressed from clinical impressions and exploratory laparotomies to histamine stimulation and phentolamine suppression tests in the 1940s, crude catecholamine measurements and iv urograms in the 1950s and 1960s, and refined measurements of catecholamine levels and computerized imaging in the 1970s and 1980s. Most laboratories now measure catecholamines by HPLC with electrochemical detection or gas chromatography and mass spectrometry. Catecholamines and their metabolites can be measured in the blood or urine.

There are major regional, institutional, and international differences in the approach to the biochemical diagnosis of pheochromocytoma. For example, at Mayo Clinic, physicians have relied on the 24-h urinary excretion of catecholamines and total metanephrines for more than 2 decades (9, 10). If the baseline 24-h urinary studies are normal, the study is repeated when the patient is symptomatic (*e.g.* with a spell). From 1976–1993, Mayo Clinic clinicians performed histamine and glucagon stimulation tests (with measurement of blood pressure and plasma fractionated catecholamines) in 542 patients in whom pheochromocytoma was highly suspected despite normal 24-h urinary catecholamine or total metanephrine excretion; none of these patients had a positive stimulation test in this setting (11). Thus, we did not find the addition of histamine and glucagon stimulation tests helpful after 24-h urinary testing. The most recent addition to the biochemical testing armamentarium is fractionated plasma free metanephrines, a test proposed to be the superior to urinary testing by some investigators (12, 13).

Herein, we focus on the biochemical tests used to diagnose sporadic adrenal pheochromocytoma. To provide perspective, two datasets from Mayo Clinic are summarized: 1) historical data before the use of fractionated free plasma metanephrines (1978–1996), and 2) current data obtained after the introduction of fractionated free plasma metanephrines (after 1998).

### *Historical data: 1978–1996*

A case-control design was used, wherein surgically confirmed cases of sporadic adrenal pheochromocytoma (n = 147) were identified by review of Mayo Clinic (Rochester, MN) medical records from 1978–1996. Controls were selected by including all nonpheochromocytoma patients who were evaluated for possible pheochromocytoma by concurrent measurements of 24-h urinary total metanephrines and catecholamines in 1995 (n = 881).

The institutional review board of Mayo Foundation approved the study, and written, informed consent of patients was acquired for review of the medical records. There was no sponsor involvement or funding for the study.

*Biochemical assays.* Twenty-four-hour urinary catecholamines were measured by liquid chromatography and electrochemical detection, whereas urinary total metanephrines were measured by spectrophotometry, both at Mayo Medical Laboratories (14–17). For 24-h urinary total metanephrines, the upper reference limit of the 95% population reference range was 3.6 $\mu$mol/24 h or more ($\geq$0.7 mg/24 h). However, based on our institutional experience to maximize specificity at an acceptable sensitivity, a urinary total metanephrine content of 6.6 $\mu$mol/24 h or more ($\geq$1.3 mg/24 h) was considered a positive result (10, 18). For urinary catecholamines, the upper reference limits of the 95% population reference range for 24-h urinary norepinephrine, epinephrine, and dopamine were 473 nmol/d (80 $\mu$g/24 h), 109 nmol/d (20 $\mu$g/24 h), and

Abbreviations: CI, Confidence interval; CT, computed tomography; MRI, magnetic resonance imaging.

2612 nmol/d (400 μg/24 h). A 24-h urinary content of norepinephrine greater than 1005 nmol/d (>170 μg/24 h), of epinephrine more than 191 nmol/d (>35 μg/24 h), or of dopamine greater than 4571 nmol/d (>700 μg/24 h) was considered positive, also on the basis of our institutional experience to maximize specificity at an acceptable sensitivity (10, 18). For the 24-h urinary total metanephrine and catecholamine test, a positive result was defined by either the urinary total metanephrine or any of the urinary catecholamine fraction measurements being increased above the set cut-off levels.

We identified 1035 cases of suspected pheochromocytoma. Of these cases, 107 were excluded because of abnormal spectral curve for metanephrines (n = 53) or lack of all three catecholamine values (n = 54), leaving a total of 928 for final analyses: 781 patients without pheochromocytoma and 147 with pheochromocytoma.

*Statistical analyses.* The 95% confidence intervals (CI) for sensitivities, specificities, positive predictive values, and negative predictive values were calculated using the Wilson method (CIA Software, London, UK). All other statistical analyses were performed using SPSS 10.0 (SPSS, Inc., Chicago, IL), including calculation of the mean and SD, comparisons of sensitivities and specificities using the McNemar test, and generation of the receiver-operating characteristic curves.

*Patients.* The 147 patients with histologically confirmed sporadic pheochromocytoma included 72 men and 75 women, with a median age of 50 yr (range, 10–81 yr). Of the 147 patients, 110 (75%) had sustained hypertension, 114 (78%) had paroxysmal symptoms (*e.g.* headaches, palpitations, diaphoresis, or tremor), and four (3%) had neither sustained hypertension nor paroxysmal symptoms.

### *Test characteristics*

*Twenty-four-hour urinary total metanephrine.* Twenty-four-hour urinary total metanephrine excretion was measured in 154 patients with pheochromocytoma. Data were not available for seven (4.5%) patients because of an abnormal spectral curve. Mean total metanephrine values were 32.4 ± 38.6 μmol/d (6.4 ± 7.6 mg/24 h). Of the 147 patients, 138 (93.9%; 95% CI, 88.8–96.7%) showed a diagnostic increase in urinary total metanephrines (≥6.6 μmol/d; ≥1.3 mg/24 h; Fig. 1 and Table 1). Nine patients (6.1%) with pheochromocytoma had a total metanephrine excretion less than 6.6 μmol/d (1.3 mg/24 h); norepinephrine and epinephrine were elevated above diagnostic cut-off levels in one patient, norepinephrine in two patients, and epinephrine in three patients. In the other three patients (2%), neither norepinephrine, epinephrine, nor dopamine was elevated above diagnostic cut-off values. These three patients had resection of an incidentally discovered adrenal mass, which was a histologically confirmed pheochromocytoma.

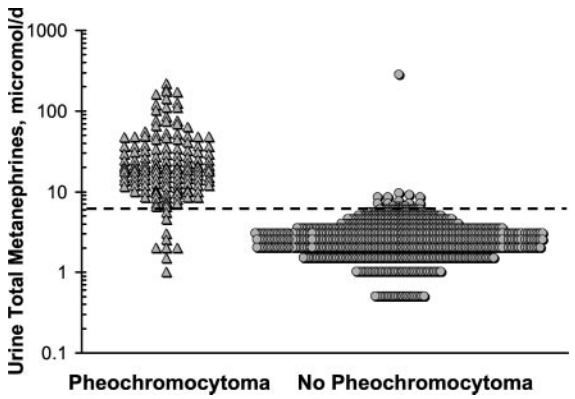


FIG. 1. Comparison of 24-h urinary excretion of total metanephrines in patients with pheochromocytoma and those without pheochromocytoma. A patient without pheochromocytoma had a markedly elevated total metanephrine value (282.4 μmol/d; 55.7 mg/24 h), which normalized when sotalol was discontinued. The *dashed line* is the diagnostic cut-off.

**TABLE 1.** Test characteristics

| | Sensitivity [% (95% CI)] | Specificity [% (95% CI)] |
|---|---|---|
| Historical data: 1978–1996 | | |
| 24-h urine | | |
| Total metanephrines | 94 (89–97) | 98 (97–99.6) |
| Norepinephrine | 61 (53–69) | 99.5 (99–99.8) |
| Epinephrine | 72 (64–79) | 99.9 (99–100) |
| Dopamine | 7 (4–12) | 99 (98.5–99.7) |
| Catecholamines | 93 (87–96) | 99.5 (98.7–99.8) |
| Metanephrines and catecholamines | 98 (94–99) | 98 (96–99) |
| More recent data (1999–2000) | | |
| Plasma | | |
| Metanephrine | 46 (28–65) | 96 (92–98) |
| Normetanephrine | 92 (74–98) | 87 (82–91) |
| Metanephrine and normetanephrine[a] | 96 (80–99) | 85 (79–89) |
| 24-h urine | | |
| Total metanephrines | 71 (51–85) | 99.6 (98–99.9) |
| Norepinephrine | 50 (31–69) | 99.6 (98–99.9) |
| Epinephrine | 29 (15–49) | 99.6 (98–99.9) |
| Dopamine | 8 (2–26) | 100 (98–100) |
| Catecholamines | 71 (51–85) | 99 (96.9–99.8) |
| Metanephrines and catecholamines[a] | 88 (69–96) | 99 (96–99.6) |

[a] Either or both measurements being above cut-offs constitutes an abnormal test result.

In 1995, 24-h urinary total metanephrines and catecholamines were measured in 927 patients without pheochromocytoma (Fig. 1). Pheochromocytoma was ultimately excluded over a 2-yr follow-up period in all patients who had unexplained false-positive results. In patients with normal results, the absence of a catecholamine-secreting tumor was based on experienced clinicians' evaluations and alternative clinical diagnoses. Data were not available for 46 (5.0%) of the patients because of an abnormal spectral curve. Spectral interference was attributed to tricyclic antidepressants in 19 patients, to labetalol in four, to sotalol in five, and to over-the-counter decongestants in three. Seventeen patients (2.0%) without pheochromocytoma had total metanephrine values of 6.6 μmol/d or more (≥1.3 mg/24 h), for a specificity of 97.8% (95% CI, 96.5–98.6%; Fig. 1). Factors that could potentially interfere with the interpretation of results were identified in 13 patients (seven were treated with tricyclic antidepressants, one was hypoglycemic during the collection period, one had severe obstructive sleep apnea, one was

treated with labetalol, one was treated with sotalol, and two were severely ill at the time of urine collection). Unexplained false positive results were noted in the other four patients (0.5%). All four patients with unexplained false positive results had normal 24-h urine values on repeat testing. The positive and negative predictive values for 24-h urine total metanephrines in the diagnosis of sporadic pheochromocytoma were 88.0% (95% CI, 83.1–93.0%) and 98.8% (95% CI, 97.8–99.4%), respectively (Table 1).

*Twenty-four-hour urinary fractionated free catecholamines.* Twenty-four-hour urinary norepinephrine, epinephrine, and dopamine levels were measured in 147 patients with pheochromocytoma (Fig. 2). The mean level was 2842 ± 3270 nmol/d (480.8 ± 553.3 μg/24 h) for norepinephrine, 914 ± 1259 nmol/d (167.4 ± 230.7 μg/24 h) for epinephrine, and 2806 ± 5785 nmol/d (429.6 ± 885.8 μg/24 h) for dopamine. The 24-h urinary norepinephrine excretion was elevated above the diagnostic cut-off value to more than 1005 nmol (>170 μg) in 90 patients (61.2%; 95% CI, 53.2–68.7%), and epinephrine was elevated to more than 191 nmol (>35 μg) in 106 (72.1%; 95% CI, 64.4–78.7%). Dopamine was increased above the diagnostic cut-off value to more than 4571 nmol (>700 μg, in 10 patients (6.8%; 95% CI, 3.7–12.1%; Table 1).

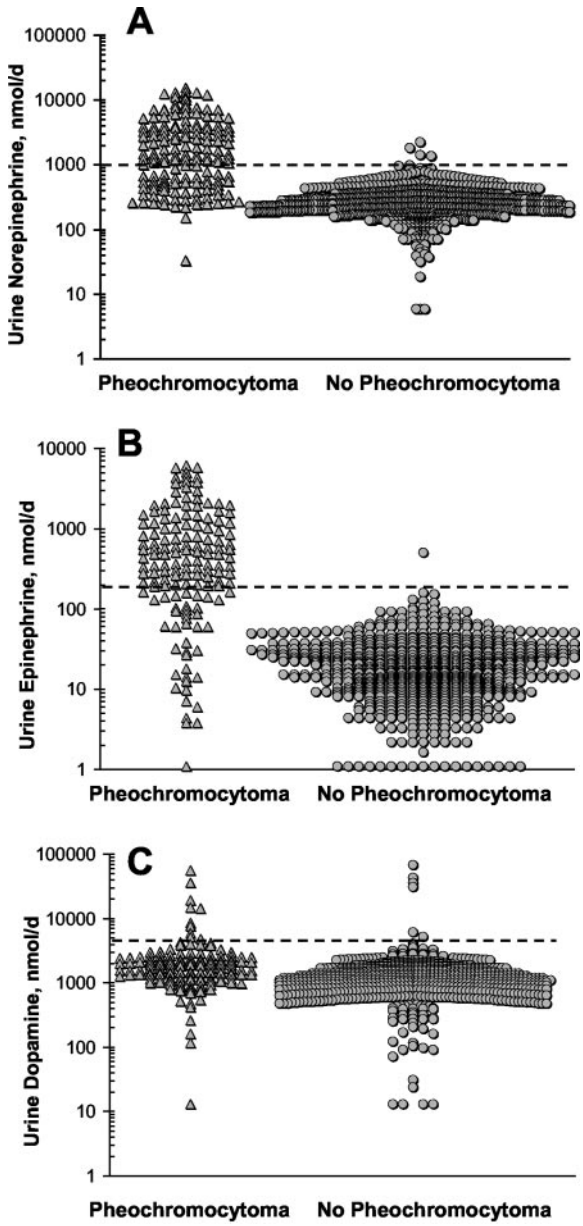


FIG. 2. Comparison of 24-h urinary excretion of norepinephrine (A), epinephrine (B), and dopamine (C) in patients with pheochromocytoma and those without pheochromocytoma. The *dashed line* is the diagnostic cut-off.

All three catecholamine values were not available for all 881 patients without pheochromocytoma in 1995. Of the patients for whom all three catecholamine values were available, four (0.5%) had norepinephrine values above the diagnostic cut-off value (>1005 nmol; >170 μg) for a specificity of 99.5% (95% CI, 98.7–99.8%; Fig. 2). Of these four subjects, interfering factors were identifiable in three (two were taking tricyclic antidepressants and one had acute intestinal ischemia), and the catecholamine levels were normal postoperatively. The positive and negative predictive values of norepinephrine in the diagnosis of sporadic pheochromocytoma were 95.7% (95% CI, 89.6–98.3%) and 93.2% (95% CI, 91.2–94.7%), respectively. Of 781 patients without pheochromocytoma, one (0.1%) had an epinephrine value above the diagnostic cut-off level (>191 nmol; >35 μg), for a specificity of 99.9% (95% CI, 99.3–100%; Fig. 2). Appropriate physiological elevation of catecholamines for severe illness (acute intestinal ischemia) was identified in this patient. The positive and negative predictive values of urinary epinephrine in the diagnosis of sporadic pheochromocytoma were 99.1% (95% CI, 94.9–99.8%) and 95.0% (95% CI, 93.3–96.6%), respectively. Of 781 patients without pheochromocytoma, six (0.8%) had dopamine values above the diagnostic cut-off level (>4571 nmol; >700 μg), for a specificity of 99.3% (95% CI, 98.5–99.7%; Fig. 2). All six of them were taking levodopa/carbidopa for the treatment of Parkinson disease. The positive and negative predictive values of urinary dopamine in the diagnosis of sporadic pheochromocytoma were 62.5% (95% CI, 38.6–81.5%) and 86.5% (95% CI, 84.2–88.4%), respectively.

The receiver-operating characteristic curves for measurements of 24-h urinary measurements of total metanephrines, norepinephrine, epinephrine, and dopamine are shown in Fig. 3.

*Sensitivity and specificity of combined 24-h urinary total metanephrines and catecholamines.* Of the 147 patients with pheochromocytoma, 136 (93%) had diagnostic excretion of norepinephrine, epinephrine, or dopamine (sensitivity, 92.5%; 95% CI, 87.1–95.8%), and 144 (98%; 95% CI, 94.2–99.3%) had either total metanephrine or catecholamine values above the diagnostic cut-off levels. The specificity of the combined urinary total metanephrine and catecholamine measurements was 97.7% (95% CI, 96.4–98.5%; Table 1). The positive and negative predictive values for the combined urinary measurement were 88.9% (95% CI, 83.1–92.9%) and 99.6% (95% CI, 98.9–99.9%), respectively. The likelihood ratio for a positive test was 42.5 (95% CI, 26.9–67.1%) for the combination of urinary total metanephrine and catecholamine measurements. The likelihood ratio for a negative test was

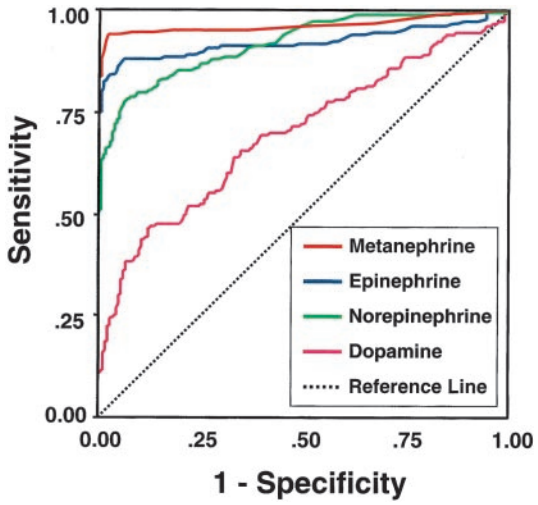


FIG. 3. Receiver-operating characteristic curves for 147 patients with pheochromocytoma and 781 without pheochromocytoma. The area under the curve (AUC) values for individual measurements were urinary total metanephrines (*red line*; AUC, 0.962; 95% CI, 0.936–10.988%; $P < 0.001$), urinary norepinephrine (*green line*; AUC, 0.917; 95% CI, 0.888–0.946%; $P < 0.001$), urinary epinephrine (*dark blue line*; AUC, 0.922; 95% CI, 0.885–0.958%; $P < 0.001$), and urinary dopamine (*purple line*; AUC, 0.697; 95% CI, 0.645–0.748%; $P = 0.001$) compared to the reference line at which the area under the curve is 0.5 (*dotted line*).

0.02 (95% CI, 0.007–0.06%) for the combination of urinary total metanephrine and catecholamine measurements.

### *Current data: Mayo Clinic experience with fractionated plasma free metanephrine measurements*

We recently reported our experience comparing the diagnostic efficacy of fractionated plasma free metanephrine measurements and measurements of 24-h urinary total metanephrines and catecholamines in patients tested for pheochromocytoma at Mayo Clinic from January 1, 1999, to November 27, 2000 (18). A subset of this database in which all patients had both plasma and 24-h urinary catecholamine and metanephrine measurements completed has been reanalyzed here. We identified 258 consecutive patients (including 24 patients with histologically confirmed pheochromocytoma or paraganglioma) in whom fractionated plasma metanephrines and 24-h urinary total metanephrines and catecholamines were measured concurrently. Six of the 24 patients had syndromic and presymptomatic pheochromocytoma (two patients had familial malignant pheochromocytoma, one had familial multiple paraganglioma syndrome, one had multiple endocrine neoplasia type 2A, one had von Hippel-Lindau syndrome, and one had multiple endocrine neoplasia type 2B).

*Biochemical assays.* Twenty-four-hour urinary catecholamines and total metanephrines were measured with the same methods used in the previous two decades, and the same positivity cut-offs were used. Liquid chromatography with electrochemical detection was used to measure fractionated plasma free metanephrines (reported as metanephrine and normetanephrine fractions) (19). All biochemical assays were performed at Mayo Medical Laboratories.

*Test characteristics.* The sensitivity of fractionated plasma metanephrine measurements was 95.8% (23 of 24 patients; 95% CI, 79.8–99.3%), compared with a sensitivity of 87.5% (21 of 24 patients; 95% CI, 69.0–95.7%) for measurements of urinary total metanephrines in combination with urinary catecholamines ($P = 0.63$). However, measurements of fractionated plasma metanephrines were significantly less specific at 84.6% (198 of 234 patients; 95% CI, 79.4–88.7%) than measurements of urinary total metanephrines and catecholamines that had a specificity of 99.7% (231 of 234 patients; 95% CI, 96.3–99.6%; $P < 0.001$; Table 1).

Of note, in patients without pheochromocytoma, we previously noted that increasing age was associated with false positive fractionated plasma metanephrine measurements ($P = 0.008$) and was correlated with increasing levels of plasma normetanephrine ($r = 0.249$; $P < 0.001$) and plasma metanephrine ($r = 0.126$; $P = 0.03$) (18). An extraadrenal paraganglioma was missed by plasma screening in one patient who had a dopamine-secreting paraganglioma of the neck and an elevated 24-h urinary dopamine level. Of the three patients with false negative urinary total metanephrine and catecholamine values, all had adrenal pheochromocytomas [two had familial syndromes (multiple endocrine neoplasia type 2A or 2B), and one had an incidentally discovered vascular adrenal mass]. None of these three patients was taking any antihypertensive medication.

## *Discussion*

The optimal approach to biochemical confirmation of catecholamine-secreting tumors is debatable (12, 13, 18, 20). There are several issues that affect the approach to diagnostic testing for pheochromocytoma. For example, test characteristics can be skewed by the inclusion of patients with presymptomatic disease who are tested solely because of their genetic predisposition to pheochromocytoma (*e.g.* multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome, neurofibromatosis type 1, or familial paraganglioma). In a commonly cited report on the sensitivity and specificity of diagnostic testing for pheochromocytoma, 36% of patients had syndromic pheochromocytoma, largely reflective of the quaternary care setting where they were evaluated (12). It is clear that fractionated plasma free metanephrines are more sensitive than 24-h urinary metanephrines and catecholamines in testing genetically predisposed patients for pheochromocytoma (12, 18). However, this finding has led to the suggestion that 24-h urinary metanephrines and catecholamines be abandoned for the less specific fractionated free plasma metanephrines when screening for pheochromocytoma in all settings (13, 21). Even if the prevalence of pheochromocytoma was estimated to be as high as one in every 200 patients screened, measurement of fractionated plasma metanephrines (with a false positive rate of ~15%) would result in 30 patients with false positive tests for every one patient with pheochromocytoma detected. Because plasma normetanephrine concentrations increase with age, elderly patients would be particularly susceptible to having false positive tests (18, 22). The potentially large number of patients with false positive biochemical tests for pheochromocytoma may be a reflection of a desire for a diagnostic

test with close to 100% sensitivity for detecting pheochromocytoma. The increased sensitivity of a diagnostic test is always at the expense of specificity. False positive tests may result in imaging studies (*e.g.* computerized tomography, magnetic resonance imaging (MRI), [$^{123}$I]metaiodobenzyguanidine scintigraphy, and positron emission tomography) being performed unnecessarily. Moreover, false positive testing results may increase patient anxiety and lead to potentially inappropriate surgery for incidental findings on imaging studies, such as benign adrenal cortical adenomas.

Clinicians should be aware of the medical disorders or medications that can interfere with the interpretation of catecholamine and metanephrine measurements. Stressful situations, such as surgery, myocardial infarction, ketoacidosis, obstructive sleep apnea, stroke, and severe heart disease, increase adrenergic activity. When catecholamines and metanephrines are measured in these situations, the diagnosis can be difficult. For at least 2 wk before the testing, patients should stop taking medications known to interfere with the interpretation of catecholamine and metanephrine measurements (Table 2). As demonstrated in the Mayo Clinic database, spectrophotometry for measuring urinary total metanephrines occasionally (5%) yields uninterpretable results (abnormal spectral curve) that may be caused by medications (*e.g.* labetalol and sotalol) or other undetermined factors. Tandem mass spectroscopy has replaced the spectrophotometry and now allows the separation of urinary metanephrine and normetanephrine, thus minimizing drug metabolite interference (23). It is anticipated that this technical advance may improve the efficacy of urinary metanephrine measurements in the diagnosis of pheochromocytoma.

The 95% reference range for a normal population is used in laboratories for determining the upper limit of normal for 24-h urinary metanephrines and catecholamines. However, the levels of metanephrines and catecholamines found in patients with spells or poorly controlled hypertension, but without pheochromocytoma, are frequently above the upper limit determined in normal value studies. To provide an acceptable level of specificity of testing, the diagnostic cutoffs for pheochromocytoma used at Mayo Clinic are approximately 2-fold higher than those for the normal population reference range. Thus, individuals with only mildly elevated or borderline elevations of urinary total metanephrines or catecholamines are not inappropriately labeled as potentially having a pheochromocytoma. The altered cut-offs used at Mayo Clinic thus result in a higher level of specificity than reported by other investigators (12). Therefore, when clinicians receive a report of 24-h urinary total metanephrine results from Mayo Medical Laboratory, if a level of 1.3 mg/24 h or more is noted, the suspicion for pheochromocytoma should be high. When clinicians review the results of 24-h urinary fractionated catecholamines, the upper limits of the reference ranges shown should be approximately doubled in interpreting a positive test.

**TABLE 2.** Medications that may cause false positive results for catecholamines and metanephrines

| |
|---|
| Tricyclic antidepressants and antipsychotics |
| Levodopa |
| Drugs containing catecholamines |
| Ethanol |
| Withdrawal from clonidine and other drugs |
| Acetaminophen and phenoxybenzamine (plasma metanephrines) |
| Major physical stress (*e.g.* surgery, stroke, obstructive sleep apnea) |

Labetalol and sotalol can interfere with the spectrophotometric assay for metanephrines; measurements of catecholamines and metanephrines are not affected by most antihypertensive agents.

The choice and interpretation of diagnostic testing may depend on the pretest level of suspicion for disease. The triggers for testing for sporadic pheochromocytoma are typically hypertension, resistant hypertension, spells, and incidental adrenal mass (18). In these settings, the 24-h urinary metanephrine and catecholamine measurements provide clinically acceptable sensitivity and significantly better specificity than fractionated plasma free metanephrine values. Of note, because of the difficulties in collecting a complete 24-h urine sample from pediatric patients, fractionated plasma free metanephrines should be considered the biochemical test of choice in that population (24).

In adults with adrenal incidentalomas, it is essential to interpret the results of biochemical testing in the context of the imaging phenotype (25, 26). Imaging phenotype refers to the characteristics of the mass on computerized imaging (25). CT and MRI findings are the best guide to the management of adrenal incidentaloma (25). The lipid-rich nature of cortical adenomas is helpful in differentiating these benign neoplasms from pheochromocytoma and malignancy (27, 28). A biochemical test that has low specificity for pheochromocytoma should be avoided when evaluating patients who have adrenal incidentalomas with a clear adrenocortical phenotype, because the imaging phenotype is not consistent with the diagnosis of a catecholamine-secreting tumor (Fig. 4A). Imaging characteristics consistent with a benign cortical adenoma include round and homogeneous density, smooth contour and sharp margination, diameter usually less than 4 cm, unilateral location, low unenhanced CT attenuation values, limited enhancement on CT with iv contrast medium, isointensity with liver on both $T_1$- and $T_2$-weighted MRI sequences, and chemical shift evidence of lipid on MRI (25–28). The imaging phenotype consistent with pheochromocytoma includes enhancement with iv contrast medium on CT, high signal intensity on $T_2$-weighted MRI, cystic and hemorrhagic changes, variable sizes, and the possibility of bilateral tumors (Fig. 4B) (25–28). For patients who have adrenal incidentaloma with an imaging phenotype suspicious for pheochromocytoma, a very sensitive biochemical test, such as fractionated plasma free metanephrines, may be helpful.

Fractionated plasma free metanephrines may be measured in a supine patient at rest for 30 min with an indwelling cannula (12, 13) or in a seated ambulatory patient with standard venipuncture (18). The supine indwelling cannula approach is not practical for most primary care office settings. The Mayo Clinic and others have favored the seated ambulatory patient approach, because it is more widely generalizable to the typical out-patient laboratory setting (18, 29). Although the normal range for fractionated free plasma metanephrines for the seated ambulatory patient approach is slightly higher than that for the supine indwelling cannula group, the sensitivity and specificity are virtually identical (12, 18).

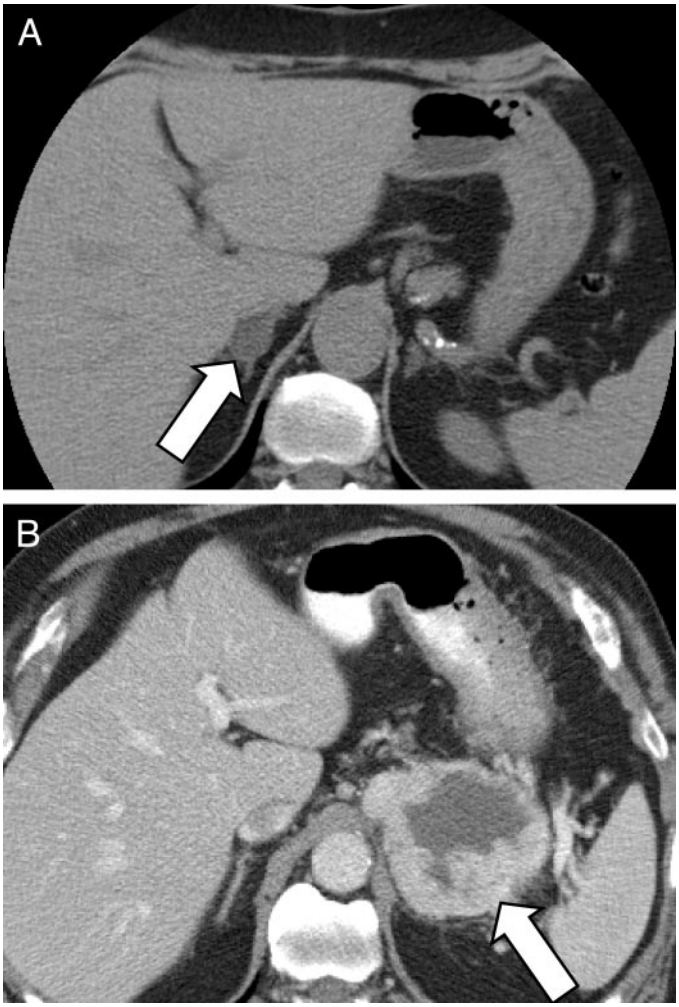


FIG. 4. CT scans of the abdomen. A, Imaging characteristics of a typical adrenocortical adenoma (*arrow*). Imaging characteristics consistent with a benign cortical adenoma include round and homogeneous density, smooth contour and sharp margination, diameter usually less than 4 cm, unilateral location, low unenhanced CT attenuation values, and limited enhancement on CT with iv contrast. B, Imaging characteristics of a typical adrenal pheochromocytoma (*arrow*) include enhancement with iv contrast medium, cystic and hemorrhagic changes, and the possibility of bilateral tumors.

Future research in biochemical testing for pheochromocytoma should include determining and validating 24-h urinary fractionated metanephrine measurements using liquid chromatography-tandem mass spectrometry (with and without measurements of fractionated catecholamines), optimizing the measurement and interpretation of fractionated plasma metanephrines (to decrease the high false positive rate), and determining which relatively low risk patients (such as those presenting with hypertension) would benefit most from screening. Mandatory mass screening of patients with hypertension may not be indicated because of the rarity of pheochromocytoma and the cost of testing.

In summary, the clinician has several options when testing for pheochromocytoma. The choice of biochemical testing for pheochromocytoma should be directed by the degree of clinical suspicion for this serious, but rare, neoplasm. High risk scenarios include patients with pallor spells, a vascular adrenal mass, a genetic syndrome that increases the risk for pheochromocytoma (*e.g.* multiple endocrine neoplasia type 2A or 2B, von Hippel-Lindau syndrome, neurofibromatosis type 1, or familial paraganglioma), a past history of pheochromocytoma, or a family history of pheochromocytoma. In these higher probability (and less common) clinical settings, a high sensitivity test that lacks specificity (*e.g.* fractionated plasma free metanephrines) and downstream imaging to exclude pheochromocytoma can be justified. However, the more common clinical scenarios are those that have a low probability of pheochromocytoma and include poorly controlled hypertension, flushing spells, palpitations, and adrenal incidentalomas with an adrenocortical phenotype. In these clinical settings, a high specificity test with acceptable sensitivity (*e.g.* 24-h urinary metanephrines and catecholamines) may be the test of choice to avoid an excessive rate of false positive tests in a low risk population.

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