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Metanephrines for Evaluating Palpitations and Flushing

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Abstract

A 29-year-old woman was referred for chronic paroxysmal palpitations, flushing, a pale complexion, and diaphoresis. She reported increasing symptoms possibly affected by stress, left lateral recumbent position, and physical activity. There was no history of weight loss, hypertension, medication use, or a family history of genetic syndromes such as von Hippel-Lindau. Physical examination revealed a body mass index of 25.9, blood pressure of 112/74 mm Hg, and a heart rate of 82 beats/min without cardiac or renal artery murmurs or skin lesions. Laboratory tests were performed (Table 1).

Test Characteristics

Twotypes of neuroendocrine tumors—pheochromocytomas (from adrenal chromaffin cells) and paragangliomas (from extra-adrenal chromaffin cells)—occur with a prevalence of approximately 0.3% among patients with hypertension.[1] The classic presentation of these tumors includes continuous or episodic hypertension, headaches, palpitations, anxiety, and pallor. These tumors may be identified via incidental discovery on imaging or by screening based on family history. Paragangliomas that are derived from the sympathetic paravertebral ganglia of the thorax, abdomen, and pelvis produce frequent catecholamines (norepinephrine and dopamine), while paragangliomas that arise from parasympathetic ganglia of the head and neck usually do not produce catecholamines. Chromaffin cells of adrenal tumors produce both epinephrine, which is metabolized to metanephrine, and norepinephrine, which is metabolized to normetanephrine. These metabolites are continuously produced from tumor cells.[2]

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Patients with a suspected pheochromocytoma or paraganglioma should undergo measurement of fractionated plasma or urinary metanephrine and normetanephrine (metanephrines).[3] Fractionated refers to a separate measurement of metanephrine and normetanephrine; a positive test is interpreted as an elevation in either. Plasma or urinary metanephrines are highly sensitive for the detection of these tumors, and combinations of these testsoffer no superiorityindetection (eTable in the Supplement).[3]TheMedicarefeesare $23.07formeasuringplasma metanephrines and $24.42 for urinary metanephrines.[4]A high diagnostic sensitivity for the detection of these tumors is achieved if blood measurements are collected in the supine position after an overnight fast and after the patient has been recumbent in aquiet room forat least 20 to 30 minutes before sampling.[3] Fractionated urinary metanephrines, with measurement of urinary creatinine forverification of collection, are preferable at centers where supine sampling is not feasible. Caffeine, smoking, and alcohol intake should be withheld for approximately 24 hours prior to testing to avoid false-positive results.

The following considerations are important when interpreting the results. Medications that raise metanephrines (Table 2), such as tricyclic antidepressants, selective norepinephrine reuptake inhibitors (less significant with selective serotonin reuptake inhibitors), or sympathomimetics may result in false-positive results and should be stopped at least 2 weeks prior to testing.[3,5] Selective α_1-adrenoceptor blockers, β-adrenoceptor blockers, diuretics, and angiotensin-convertingenzyme inhibitors may have little influence on biochemical testing and can be continued.[5] Medications that interfere with biochemical testing should only be stopped if safe and noninterfering alternatives can be substituted. Stress, illness, strenuous physical activity, or withdrawal from drugs (eg, opioids, benzodiazepines), alcohol, or smoking may markedly elevate metanephrines or catecholamines.[3] Testing after excluding these sources of false-positive results is useful.[3]

Levels of metanephrines more than 3-fold above the upper limitof the age-adjusted reference interval are rarely false-positive results.[3] Levels of metanephrines within the reference range exclude these tumors, while equivocal results (<3-fold above the upper limit) require additional tests provided that reference intervals have been appropriately established and measurement methods are accurate and precise.[3,5] False-negative metanephrines could be observed in tumors that are smaller than 1 cm, dopamine-secreting head and neck tumors (methoxytyramine, a metabolite of dopamine, is preferentially measured), or nonfunctional tumors.[5] Normal catecholamines may help exclude false-positive results.

Application of Test Results to This Patient

The patient presented with classic symptoms of pheochromocytoma or paraganglioma. The significant elevations in plasma normetanephrines were highly consistent with either tumor.[3] Abdominal magnetic resonance imaging showed a 6.3 × 4.8-cm left adrenal mass with bright signals on T2-weighted images, consistent with pheochromocytoma. Imaging of these tumors should not be performed until a biochemical diagnosis has been established.

What Are Alternatives to Initial Screening Tests?

Initial testing should always include measurements of metanephrines (has superior sensitivity for detecting these tumors over plasma catecholamines [Medicare fee, $34.14], urinary catecholamines [Medicare fee, $23.42], and urinary vanillylmandelic acid [Medicare fee, $26.36]; eTable in the Supplement).[4,6] Negative results for plasma metanephrines obtained while a patient is seated are as effective for ruling out tumors as negative results while supine,[7] but seated testing can lead to a 5.7-fold increase in false-positive results.[8]

Patient Outcome

Thepatient started a selective α_1-adrenoceptor blocker 2 weeks before surgery, given the elevated normetanephrines. She underwent a laparoscopic left total adrenalectomy without complications. Since these tumors carry the highest degree of heritability in human neoplasms, genetic testing was performed and revealed no mutations. One month later, plasma normetanephrines returned (in normal range) and symptoms resolved.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HOW DO YOU INTERPRET THESE TEST RESULTS?

A. Adrenocortical carcinoma; proceed with biopsy.

B. Pheochromocytoma; proceed with imaging studies.

C. Aldosterone-producing adenoma; refer for surgery.

D. False-positive results; repeat testing.

B. Pheochromocytoma; proceed with imaging studies.

Clinical Bottom Line

- Metanephrines are the preferred initial biochemical test for pheochromocytomas and paragangliomas and consist of fractionated plasma or urinary metanephrine or normetanephrine.
- Metanephrines have higher sensitivity than plasma or urinary catecholamines as diagnostic tests for pheochromocytoma and paraganglioma.
- Plasma metanephrines should be collected in the supine position after the patient has been recumbent (quiet room, 20–30 min).
- Interfering medications should only be stopped if safe and noninterfering alternatives can be substituted.
- Metanephrine values within normal range exclude pheochromocytoma and paraganglioma.

Table 1.

Laboratory Test Results

Laboratory Test	Patient's Values	Reference Range
Sodium, mEq/L	140	136–145
Potassium, mEq/L	3.9	3.4–5.1
Total carbon dioxide, mEq/L	30	22–29
Creatinine, mg/dL	0.63	0.51–0.95
Plasma renin activity, ng/mL/h	2.1	≤0.6–3.0
Plasma aldosterone concentration, ng/dL	8.6	≤26.0
Thyrotropin, (TSH), mIU/mL	1.04	0.27–4.20
Calcium, mg/dL	9.04	8.6–10.2
Fractionated[a] plasma metanephrines		
Metanephrine, pg/mL	42	12–61
Normetanephrine, pg/mL	5258	18–112

SI conversion factors: calcium to mmol/L, multiply by 0.25; creatinine to μmol/L, multiply by 88.4; plasma aldosterone concentration to pmol/L, multiply by 27.74.

[a]Indicates a separate measurement of metanephrine and normetanephrine. Adult reference ranges are provided.

Table 2.

Medications That Interfere With Testing of Fractionated Plasma or Urinary Metanephrines

	Metanephrine	Normetanephrine
Acetaminophen[a]	-	↑↑
α-Methyldopa[a]	-	↑↑
Tricyclic antidepressants	-	↑↑
Mesalamine[a]/sulfasalazine[a]	-	↑↑
Phenoxybenzamine	-	↑
Monoamine oxidase inhibitors[b]	↑↑	↑↑
Sympathomimetics[b]	↑	↑
Cocaine[b]	-	↑↑
Levodopa[a,c]	↑	↑

Symbols: ↑↑, clear increase (≥3-fold above the upper limit depending on the dose and duration of administration); ↑, mild increase (<3-fold above the upper limit); -, no increase. Adapted from Lenders et al.[3]

[a]Whether these drugs interfere with the measurement or elevate fractionated plasma or urinary metanephrines depends on the assay and should be withdrawn 5 days before testing. Drug interference is not an issue when mass spectometry–based assays are used.

[b]Monoamine oxidase inhibitors, sympathomimetics, and cocaine can increase catecholamines (thereby metanephrines through peripheral conversion).

[c]Levodopa elevates dopamine and thereby methoxytyramine (its measured metabolite), which elevates metanephrine and normetanephrine using non–mass spectrometry-based assays.