



1-MINUTE CONSULT

Hiba Z. Hashmi, MD

Department of Medicine, Division of Diabetes, Endocrinology, and Metabolism, University of Minnesota, Minneapolis, MN

Muhammad Arslan Arif Maan, MD

Department of Hospital Medicine, UnityPoint Health-St Luke's Hospital, Cedar Rapids, IA

Laura LaFave, MD

Division Director, Department of Medicine, Division of Diabetes, Endocrinology, and Metabolism, Hennepin County Medical Center, Minneapolis, MN

BRIEF
ANSWERS
TO SPECIFIC
CLINICAL
QUESTIONS

Q: What is the rationale for the laboratory workup for suspected pheochromocytomas and paragangliomas?

A: Selection of screening tests for pheochromocytomas and paragangliomas (PPGLs) is best guided by high clinical suspicion. Test results should be interpreted with careful consideration of collection methods before pursuing imaging tests for localization or referring for endocrinologic evaluation.

PPGLs are rare neuroendocrine tumors, with an estimated incidence of 2 to 8 per million.¹ These catecholamine-secreting chromaffin cell tumors are mostly benign² but can manifest as metastatic disease in 15% to 17% of cases.¹ Pheochromocytomas arise from chromaffin cells of the adrenal medulla, and paragangliomas arise from extra-adrenal chromaffin cells of sympathetic or parasympathetic origin. The prevalence of PPGLs in patients presenting with hypertension in the outpatient setting is 0.1% to 0.6%.^{1,3} However, PPGLs can be asymptomatic and discovered incidentally on imaging. Of these incidentalomas, 80% to 85% are pheochromocytomas, and 15% to 20% are paragangliomas.^{1,3} While the parasympathetic nervous system of the head and neck can also give rise to paragangliomas, tumors in this location do not produce vasoactive amines.¹

CLINICAL PRESENTATION

Clinical features are key in diagnosing PPGLs.² The kaleidoscope of clinical presentations is dominated by signs and symptoms that indicate an overactive sympathetic autonomic nervous system (**Table 1**).^{3,4}

doi:10.3949/cjfm.90a.20197

Palpitations, hyperhidrosis, and headaches form the classic triad of symptoms with a combined specificity of 93.8%,⁵ but there are distinguishing factors. For example, palpitations, hyperhidrosis, tremors, pallor, and nausea are the most frequently reported symptoms in patients with PPGLs, with one or more occurring in 85% of patients, and their presence may help distinguish patients with PPGLs from those without PPGLs.⁴ Despite the typical symptoms occurring in 85% of patients, incidentalomas noted on computed tomography and genetic case-detection testing lead to up to 62% of diagnoses.⁶

CONSEQUENCES OF CATECHOLAMINES

Catecholamines—including the “fight or flight” hormones epinephrine, norepinephrine, and dopamine—are secreted in response to stress. In healthy people, catecholamine levels after myocardial infarction may be 10 to 20 times higher than at baseline.^{2,7} Hypertension, a key characteristic of PPGLs, is precipitated by high catecholamine levels. Norepinephrine and epinephrine increase cardiac output through beta-receptor activity and increase peripheral vascular resistance through alpha-receptor activity. Paroxysmal release of catecholamines results in mostly episodic hypertension, with some patients normotensive between episodes and others experiencing sustained hypertension.³

Dopamine production targets D1 and D2 receptors. D1 receptor activation results in renal vasodilation, and D2 activation inhibits norepinephrine

secretion from sympathetic nerve terminals, which has a negative inotropic effect on the heart. This explains why some patients with dopamine-secreting PPGLs present only with hypotension.^{8,9} Orthostatic hypotension in a patient with a history of hypertension is a good clinical clue for PPGLs.³ The overall balance of vasoconstrictive vs vasodilatory effects of the unique hormonal cocktail produced by the tumor determines the tumor's clinical behavior.

■ INITIAL BIOCHEMICAL TESTING: FOCUS ON SENSITIVITY

A missed diagnosis of PPGLs can have devastating cardiovascular consequences, including myocardial infarction, cardiac arrhythmias, heart failure due to toxic cardiomyopathy, and pulmonary edema. The initial biochemical testing methods should therefore focus on maximizing sensitivity.

Biochemical testing for pheochromocytoma is indicated in patients who have symptoms of catecholamine excess, an adrenal incidentaloma, or a hereditary predisposition to development of PPGLs.⁹

In contrast to episodic catecholamine release, the products of catecholamine metabolism are constantly released from PPGLs into the circulation. Metabolic products of catecholamines have longer plasma half-lives and are therefore easier to measure. Hence, plasma free metanephrines or 24-hour urinary fractionated metanephrines should be the initial investigative tests to rule out PPGLs.^{2,9} Levels of dopamine and its metabolite plasma 3-methoxytyramine can help establish the biochemical subtype of PPGL but are not essential for initial screening.²

The diagnostic sensitivity of plasma free metanephrines is above 96% and the specificity is about 89%. The sensitivity of 24-hour urinary fractionated metanephrines is 86% and specificity is above 69%.² The sensitivities and specificities reported in the literature vary depending on the assays used. Plasma tests using liquid chromatography with tandem mass spectrometry afford higher sensitivity and specificity than immunoassays.² Mass spectrometry methods employed in urine testing are also more sensitive and specific than other techniques.²

Some studies have claimed to demonstrate that measuring plasma free metanephrines has a higher specificity than 24-hour urinary fractionated metanephrines,² but robust, direct comparisons using the gold standard of mass spectrometry to establish this are lacking. Therefore, the Endocrine Society and the North American Neuroendocrine Tumor Society

TABLE 1

Symptoms of pheochromocytomas and paragangliomas

Most frequent	Most specific (classic triad)	Less frequent
Palpitations	Palpitations	Anxiety or panic
Hyperhidrosis	Hyperhidrosis	Weight loss
Tremors	Headaches	Fatigue
Pallor		Constipation
Nausea		

Based on information in references 3 and 4.

guidelines recommend initial screening with either plasma free metanephrines or urinary fractionated metanephrines.^{2,9}

■ HOW THE SAMPLE IS COLLECTED IS KEY

For accurate results, the blood sample for plasma free metanephrines must be collected by an indwelling catheter placed 30 minutes prior to the draw, and the patient must be in a supine position for the full 30 minutes. A sample collected under these conditions can be a powerful tool for diagnosing PPGLs, with newer studies reporting a false-positive rate of less than 3% with proper collection, and superiority over 24-hour urine collection.¹⁰

Testing of plasma free metanephrines is preferred over urine fractionated metanephrines in patients with renal dysfunction, but many laboratory collection sites do not have time, expertise, or resources to follow the protocol required for the blood draw. Therefore, 24-hour urine collection may be a more accurate, although time-consuming, option. Emerging studies have noted that the sensitivity and specificity of spot urine samples correlate well with those of 24-hour samples, but at present the evidence is insufficient to recommend adopting this strategy in routine clinical practice.^{2,11}

Vanillylmandelic acid has poor sensitivity and is not indicated in the initial biochemical workup for possible PPGLs.¹²

■ DIAGNOSTIC INTERPRETATION

A 3-fold to 4-fold rise above the upper limit of normal for plasma free metanephrines or urinary fractionated metanephrines is unlikely to be a false-positive result. Metanephrine levels within the reference range are

TABLE 2
Medications associated with false-positive screening tests

Class	Name
Antihypertensive	Beta-blocker (labetalol, sotalol)
	Alpha-2 agonist (alpha-methyldopa)
	Alpha-2 antagonist (phenoxybenzamine)
	Alpha, beta-1, beta-2 agonist (ephedrine)
	Calcium channel blocker (dihydropyridines)
Stimulant	Caffeine
	Nicotine
	Amphetamine
	Cocaine
Anxiolytic	Buspirone
Analgesic	Acetaminophen
Anti-inflammatory	Sulfasalazine
Antidepressant	Tricyclic antidepressants
	Monoamine oxidase inhibitors
Dopamine agonist	Levodopa

Based on information in references 3 and 4.

usually sufficient to exclude PPGLs. But importantly, very small tumors (< 1 cm) or dopamine-secreting tumors can result in false-negative results.²

Fasting blood levels of plasma 3-methoxytyramine should be measured to evaluate for dopamine-secreting PPGLs if initial metanephrine testing is negative but the index of clinical suspicion for PPGL remains high.²

■ EQUIVOCAL RESULTS: WHAT IS NEXT?

An equivocal test result (ie, metanephrine elevation to less than 3 times the upper limit of reference range) indicates a need for further workup and questions:

- **Was the blood or urine screening sample collected appropriately?** Caffeinated beverages, alcohol intake, smoking, and intense physical activity can cause false-positive results and should

be avoided at least 24 hours prior to test collection.¹ Several medications (Table 2)^{3,4} can also skew the results if not withheld before the sample is drawn. Acetaminophen should ideally be held for 5 days before sample collection. Given that the false-positive rate is not very high with antihypertensive medications, these can be continued at the time of test collection unless a repeat test is being performed for confirmation of a prior equivocal test.¹³ If the patient is taking monoamine oxidase inhibitors, stimulants, or tricyclic antidepressants, the medication should be stopped at least 2 weeks before biochemical testing for PPGLs.¹⁴

- **Was the patient under physiologic stress at the time of collection?** Screening tests are likely to be falsely positive during critical illness. In this setting, the test should be repeated when clinical stability is achieved.
- **Are the results still equivocal?** A clonidine suppression test can be considered. This test, shown to be highly specific,^{2,9} involves measurement of baseline serum normetanephrine levels followed by clonidine administration with a repeat draw and measurement 3 hours later. If serum normetanephrine levels are elevated or decrease by less than 40%, PPGL is likely. Clonidine, an alpha-receptor agonist, inhibits norepinephrine release in patients without autonomous production of catecholamines but not in patients with PPGLs.

If the patient has a low pretest probability of having PPGLs, then a screening test can be repeated in 6 months to assess the trend. This would help identify a small tumor that may be enlarging over time.

■ TAKE-HOME POINTS

The rationale for timely diagnosis of PPGLs relies on a high index of suspicion and awareness of clinical features. Appropriate collection methods, testing that prioritizes high sensitivity, and careful review of findings will support the diagnostic process. ■

■ DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Aygun N, Uludag M.** Pheochromocytoma and paraganglioma: from epidemiology to clinical findings. *Sisli Etfal Hastan Tip Bul* 2020; 54(2):159–168. doi:10.14744/SEMB.2020.18794
2. **Lenders JW, Duh QY, Eisenhofer G, et al.** Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2014; 99(6):1915–1942. doi:10.1210/jc.2014-1498
3. **Lenders JW, Eisenhofer G, Mannelli M, Pacak K.** Pheochromocytoma. *Lancet* 2005; 366(9486):665–675. doi:10.1016/S0140-6736(05)67139-5
4. **Geroula A, Deutschbein T, Langton K, et al.** Pheochromocytoma and paraganglioma: clinical feature-based disease probability in relation to catecholamine biochemistry and reason for disease suspicion. *Eur J Endocrinol* 2019; 181(4):409–420. doi:10.1530/EJE-19-0159
5. **Plouin PF, Degoulet P, Tugayé A, Ducrocq MB, Ménard J.** Screening for pheochromocytoma: in which hypertensive patients? A semiological study of 2585 patients, including 11 with pheochromocytoma (author's transl). *Nouv Presse Med* 1981; 10(11):869–872. [French.] PMID:7208288
6. **Gruber LM, Hartman RP, Thompson GB, et al.** Pheochromocytoma characteristics and behavior differ depending on method of discovery. *J Clin Endocrinol Metab* 2019; 104(5):1386–1393. doi:10.1210/jc.2018-01707
7. **Gardner D, Shoback D.** Greenspan's Basic and Clinical Endocrinology. 10th ed. McGraw Hill Education; 2017.
8. **Bozin M, Lamb A, Putra LJ.** Pheochromocytoma with negative metanephrines: a rarity and the significance of dopamine secreting tumors. *Urol Case Rep* 2017; 12:51–53. doi:10.1016/j.eucr.2017.02.002
9. **Chen H, Sippel RS, O'Dorisio MS, et al.** The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. *Pancreas* 2010; 39(6):775–783. doi:10.1097/MPA.0b013e3181ebb4f0
10. **Kline GA, Boyd J, Polzin B, et al.** Properly collected plasma metanephrines excludes PPGL after false-positive screening tests. *J Clin Endocrinol Metab* 2021; 106(8):e2900–e2906. doi:10.1210/clinem/dgab241
11. **Sbardella E, Maunsell Z, May CJH, et al.** Random 'spot' urinary metanephrines compared with 24-h-urinary and plasma results in pheochromocytomas and paragangliomas. *Eur J Endocrinol* 2020; 183(2):129–139. doi:10.1530/EJE-19-0809
12. **van Berkel A, Lenders JW, Timmers HJ.** Diagnosis of endocrine disease: biochemical diagnosis of pheochromocytoma and paraganglioma. *Eur J Endocrinol* 2014; 170(3):R109–R119. doi:10.1530/EJE-13-0882
13. **Eisenhofer G, Goldstein DS, Walther MM, et al.** Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. *J Clin Endocrinol Metab* 2003; 88(6):2656–2666. doi:10.1210/jc.2002-030005
14. **Neumann HPH, Young WF Jr, Eng C.** Pheochromocytoma and paraganglioma. *N Engl J Med* 2019; 381(6):552–565. doi:10.1056/NEJMra1806651

Address: Hiba Z. Hashmi, MD, Department of Medicine, Division of Diabetes, Endocrinology, and Metabolism, University of Minnesota, 516 Delaware Street SE, MMC 101, Minneapolis, MN 55455; hashm026@umn.edu