
Biochemical Diagnosis of Pheochromocytoma and Paraganglioma

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Abstract: Pheochromocytoma and paraganglioma are catecholamine-secreting neuroendocrine tumors that arise from chromaffin cells of the adrenal glands and paraganglia. In the absence of timely diagnosis and treatment, overproduction of catecholamines by these tumors can have devastating consequences. Biochemical confirmation of excessive catecholamines and their metabolites is essential for the definitive diagnosis of pheochromocytoma and paraganglioma and proper patient management. This chapter reviews catecholamine biology, biochemical phenotypes, choice of biochemical tests, analytical methods, sampling, storage, and interpretation of the results.

Keywords: Catecholamines; Dopamine; Epinephrine; Metanephrine; Norepinephrine

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INTRODUCTION

Overproduction of catecholamines commonly accompanies the development of pheochromocytoma (PCC) and paraganglioma (PGL). Thus, catecholamines excess provides a powerful biochemical evidence for the diagnosis of PCC/PGL (PPGL) (1–3). Accurate measurement of catecholamines and their metabolites is the first crucial step for the diagnosis of PPGL and patient management (4). With the development of analytical technologies, these biomarkers for PPGL can be determined using several biochemical methods, and the choice of the best method is an issue worthy of discussion (5). An understanding of PPGL biochemical testing, including catecholamine biology, biochemical phenotypes, choice of tests, analytical methods, sampling, storage, and interpretation of results, is of great significance for clinical decision-making.

CATECHOLAMINES BIOLOGY

Catecholamines, including epinephrine, norepinephrine, and dopamine, constitute a class of chemical neurotransmitters and hormones that occupy important positions in the regulation of physiological processes and are involved in the development of neurological, psychiatric, endocrine, and cardiovascular diseases (6). The metabolism of catecholamines takes place within the cytoplasm of the neuronal or endocrine cells where catecholamines are synthesized. The vesicular stores of catecholamines are in a dynamic equilibrium with the cytosolic pool, and leakage of catecholamines from vesicular granules into the cytoplasm is counterbalanced by inward active sequestration back into stores via vesicular monoamine transporters (7). The metabolism of catecholamines involves primarily two enzymes: monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT), which compete with the vesicular monoamine transporters to inactivate cytoplasmic catecholamines (8). Thus, under resting conditions, catecholamine metabolism is mostly a passive process of vesicular leakage than the active process of exocytosis followed by cellular uptake. Generally, in the metabolic processing of catecholamines, epinephrine (E), norepinephrine (NE), and dopamine (DA) are converted into metanephrine (MN), normetanephrine (NMN), 3,4-dihydroxyphenylglycol (DHPG), 3,4-dihydroxyphenylacetic acid (DOPAC), and 3-methoxytyramine (3-MT) by MAO or COMT, and are terminally metabolized to vanillylmandelic acid (VMA) and homovanillic acid (HVA) (Figure 1). VMA is the end product of E and NE, and HVA is the principal product of DA (9). In addition, DA can also act as the biosynthetic basis for the production of NE under dopamine- β -hydroxylase (DBH) catalyzation and further conversion to E under phenylethanolamine-N-methyltransferase (PNMT) catalysis (6, 7, 10).

Sympathetic nerves contain MAO, but not COMT (4). The substantial production of DHPG from norepinephrine in sympathetic nerves obscures the relatively small increase in DHPG due to tumor cells; thus, DHPG is an insensitive marker of PPGL. Substantial production of VMA from hepatic uptake and metabolism of circulating DHPG and MHPG also make VMA a poor choice. Given that about 80% of all PPGLs arise from the adrenal medulla (11), catecholamine

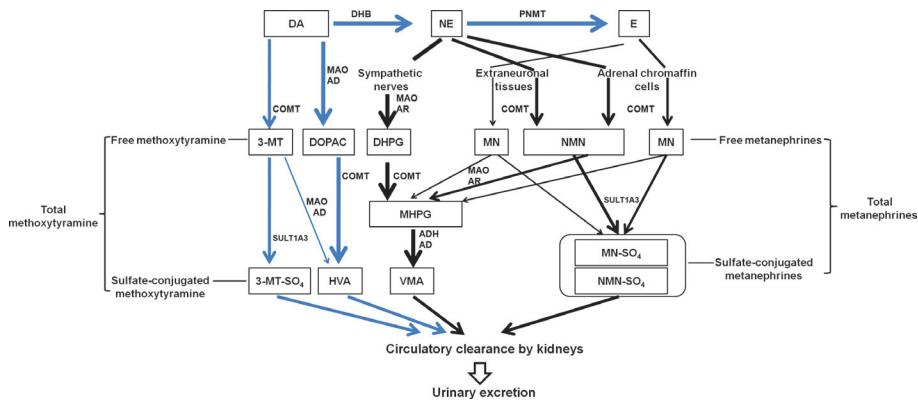


Figure 1 Metabolic pathway of catecholamines. 3-MT, 3-methoxytyramine; 3-MT-SO₄, 3-methoxytyramine sulfate; ADH, alcohol dehydrogenase; AD, aldehyde reductase; AR, aldehyde dehydrogenases; COMT, catechol-O-methyltransferase; DA, dopamine; DBH, dopamine β -hydroxylase; DHPG, 3,4-dihydroxyphenylglycol; DOPAC, 3,4-dihydroxyphenylacetic acid; E, epinephrine; HVA, homovanillic acid; MAO, monoamine oxidase; MHPG, 3-methoxy-4-hydroxyphenylglycol; MN, metanephrine; MN-SO₄, metanephrine-sulfate; NE, norepinephrine; NMN, normetanephrine; NMN-SO₄, normetanephrine sulfate; PNMT, phenylethanolamine-N-methyltransferase; SULT1A3, sulfotransferase type 1A3; VMA, vanillylmandelic acid.

O-methylation in the adrenal medulla is the predominant source of MN and NMN, which are produced continuously and independently of catecholamine release. As a result, O-methylated metabolites provide selective and superior biomarkers of catecholamine metabolism in adrenal medullary cells versus neurons. Although tumors that predominantly produce DA due to lack of DBH are occasional, DA metabolism should also be considered for the diagnosis of dopamine-secreting tumors (12). In contrast to sympathetic nerves, adrenal chromaffin cells contain both MAO and COMT. In the adrenal gland, DA is first O-methylated by COMT to 3-MT; subsequently, 3-MT is metabolized by MAO to HVA (9). As MN and NMN, 3-MT is a superior diagnostic biomarker relative to its parent catecholamine and the final metabolic products.

BIOCHEMICAL PHENOTYPES

The biochemical phenotypes of PPGs are characterized by the hypersecretion of different combinations of catecholamines. Some PPGs produce only NE, some secret both NE and DA, some produce both E and NE, and rare tumors secret solely E or DA (4). This can be related to the genetic background of the tumors. In patients with *von Hippel-Lindau (VHL)* gene mutations, the tumors can be adrenal or extra-adrenal and overproduce only NE, regardless of location. *VHL*-related PPGs always present at an early age and are occasionally malignant. PPGs from patients with mutations in the genes encoding the subunits B and D of succinate dehydrogenase (*SDHB* and *SDHD*) are characterized by hypersecretion of DA, either with or without NE. These tumors usually arise in extra-adrenal locations,

representing 19–28% of the head and neck PPGPs, can manifest malignant tendency, and present at an early age (13). Generally, the above-mentioned noradrenergic or dopaminergic tumors are partitioned in cluster 1 (including *VHL* and *SDH* mutations), whereas the adrenaline-producing tumors are partitioned in cluster 2. The cluster 2 comprises multiple endocrine neoplasia type 2 (*MEN* 2) and neurofibromatosis type 1 (*NF1*) patients, who almost always present at comparatively late age with intra-adrenal tumors that are rarely malignant and secrete both E and NE (7, 14). Thus, in addition to disease stratification, the biochemical phenotypes can provide useful information to prioritize gene selection for genetic testing. PPGL patients lacking symptoms of catecholamine excess pose a significant diagnostic challenge. The diagnosis of biochemically silent tumors that do not produce catecholamines is sometimes delayed, with higher risk of advanced metastatic disease. In this respect, *SDHB*-related extra-adrenal abdominal PPGLs are sometimes biochemically silent (15, 16). The determination of circulating chromogranin A (CgA), an acid-soluble protein co-released with catecholamines, may provide an alternative biochemical parameter for the screening of suspected PPGL patients presenting normal catecholamine levels (16).

CHOICE OF TESTS

The biochemical screening of PPGLs usually involves the measurement of urinary and plasma catecholamines, urinary fractionated metanephries, plasma free metanephries, and urinary VMA. Given that PPGL is fatal if undiagnosed, it is important that the biochemical tests used for screening possess a high degree of sensitivity and specificity. The recommended initial test can include the determination of either plasma free metanephries or urinary fractionated metanephries, but not of catecholamines themselves (17, 18). In fact, unlike catecholamines, which are only secreted episodically and have relatively short half-life, metanephries as their metabolic intermediates have relatively longer plasma half-lives (5). Furthermore, plasma metanephrine secretion is relatively uninfluenced by sympathoadrenal excitation (9, 19). Therefore, either the measurement of plasma free metanephries or the measurement of urinary fractionated metanephries provides a highly sensitive assay for PPGLs detection (20–23).

It has been suggested that in young patients, and in outpatients, plasma specimens should be preferred to 24-h urine collection, due to their simpler and more rigorous control (24). Statistical evidence that the measurement of plasma free metanephries and urinary fractionated metanephries provides advantages over other tests has been presented in many studies (21, 23–27). The measurement of plasma free metanephries is reported to have a sensitivity of 99% and a specificity of 89% (28–30). The sensitivity and specificity reported for the urinary metanephries assay are lower, that is, 97 and 69% (31), and those of the plasma catecholamines assay are 84 and 81%, respectively. For urinary catecholamines, the sensitivity is 86% and the specificity is 88% (31). The determination of VMA in urine has acceptable specificity (95%) but relatively low sensitivity (64%), while total urinary metanephries have similar specificity but higher sensitivity (i.e., 77%) (32). The characteristics of biochemical tests are summarized in Table 1 (33–49). While it is evident that the determination of plasma free metanephries

TABLE 1 Characteristics of the different biochemical tests used for the diagnosis of PPGLs

Reference	Methods	Items	URL	Sensitivity (%)	Specificity (%)	Subjects
33	LC-MS/MS HPLC-ECD	PFM:MN/NMN (Seat) PFM:MN/NMN (Seat)	0.47/1.1 nmol/L 0.50/0.90 nmol/L	ND ND	ND ND	58 58
34	LC-MS/MS	UFM:MN/NMN, 24h	1.53/1.40/0.1 nmol/24h	97.1 (99/102)	90.8 (367/404)	506
35	LC-ECD	PFM:MN/NMN (Spine)	0.31/0.61 nmol/L	1.00 (25/25)	96.7 (1194/1235)	1260
36	HPLC-ECD	PFM:MN/NMN PC	0.5/0.9 nmol/L ND	1.00 78.6	97.6 70.7	55 55
	UFM, 24h	ND	ND	85.7	95.1	55
	UC, 24h	ND	ND	78.6	87.8	55
	UV, 24h	ND	ND	93.0	75.6	55
37	LC-MS/MS ELISA	PFM:MN/NMN (Seat) PFM:MN/NMN (Seat)	0.51/1.18 nmol/L 0.45/71.09/2 nmol/L	100 (38/38) 95 (36/38)	96 (5/113) 95 (6/113)	151 151
38	LC-MS/MS	UFM:MN/NMN, 24h	1.75/1.45/33 nmol/24h	ND	ND	127
39	LC-MS/MS	PFM:MN/NMN	0.49/0.89 nmol/L	ND	ND	45
40	HPLC-ECD	UFM:MN/NMN, 24h	350/650 nmol/24h	ND	ND	29
	HPLC-ECD	UV, 24h	<35 µmol/24h	ND	ND	29
41	HPLC-ECD	PFM:MN/NMN(Spine)	0.33/0.65 nmol/L	97 (193/198)	93 (493/528)	726
42	LC-MS/MS	PFM:MN/NMN(Spine)	0.41/0.79 nmol/L	1.00 (62/62)	95.0 (416/438)	762
43	LC-MS/MS	PFM:MN/NMN	0.51/1.18 nmol/L	94.4 (34/36)	96.5 (164/170)	206

Table continued on following page

TABLE 1 Characteristics of the different biochemical tests used for the diagnosis of PPGLs (Continued)

Reference	Methods	Items	URL	Sensitivity (%)	Specificity (%)	Subjects
44	LC-MS/MS	PFM:MN/NMN(Supine)	88/200 pg/mL	98.1 (53/54)	99.7 (286/287)	341
	EIA	PFM:MN/NMN(Supine)	90/180 pg/mL	74.1 (40/54)	98.9 (284/287)	341
45	LC-MS/MS	UV, 24h	<35.0 pmol/24h	ND	ND	160
46	LC-MS/MS	PFM:MN/NMN	0.69/1.58 nmol/L	ND	ND	121
47	RIA	PFM:MN/NMN(Supine)	100/170 ng/l	96	100	55
		CGA(Supine)	150ug/l	93	96	55
48	LC-MS/MS	PFM:MN/NMN(Supine)	0.45/1.09 nmol/L	97.2 (207/213)	95.9 (1641/1712)	1963
49	LC-MS/MS	UC:ENE/DA	16.7/101.1/443.3 ug/24h	ND	ND	310

CGA, chromogranin A; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; ND, no data; PC, plasma catecholamines; PFM, plasma free metanephrine; RIA, radioimmunoassay; UC, urinary catecholamines; UFM, urinary fractionated metanephrines; URL, upper reference limit; UTM, urinary total metanephrines; UV, urine VMA.

and the determination of urinary fractionated metanephrenes are superior methods, the choice of one method over the other is debated (4). A combination of tests could provide a better diagnosis by improving sensitivity and specificity and reducing false positive and false negative results. In addition, the measurement of the plasma concentrations of CgA is sometimes used, especially for silent PPGLs. Importantly, CgA levels are not influenced by the drugs commonly used for PPGLs treatment (20). It is worth noting that emphasis on initial biochemical testing of MN and NMN might make the detection of tumors that produce exclusively DA difficult. Therefore, the O-methylated metabolite of DA, 3-methoxytyramine, should be measured together with MN and NMN for improved accuracy, particularly when screening for *SDHB* and *SDHD*-associated PPGLs, often characterized by increased DA, with or without NE increase (4). It is recommended that initial biochemical testing for PPGLs should include the measurement of plasma free metanephrenes and/or urinary fractionated metanephrenes. The reference intervals vary with the analytical method, and clinical laboratories should establish their own reference intervals.

ANALYTICAL METHODS

The analytical methods for the evaluation of catecholamines and their metabolites have undergone rapid developments, from simple colorimetric detection to advanced high-performance liquid chromatography (HPLC)-based techniques incorporating electrochemical, fluorometric, and mass spectrometric analyses (50, 51). In the early days, colorimetric and fluorometric methods utilized ultraviolet or fluorescent derivatizing agents that reacted with the analytes to produce ultraviolet light or fluorescence (52, 53). These methods, however, had poor sensitivity and selectivity, with complicated derivatization processes, and in the 1970s these were quickly replaced by radioenzymatic assays based on enzymatic O-methylation of the catechol ring with a tritium-labeled methyl donor, S-adenosylmethionine (54–56). However, radioenzymatic methods had their own disadvantages, including complexity and length of the procedures and high intra- and inter-laboratory variability, which limited their use in routine clinical laboratory settings.

HPLC coupled with electrochemical (HPLC-ECD) or fluorometric (HPLC-FLD) detection is presently the most promising and widely used technique for simultaneous quantification of plasma or urinary catecholamines and their metabolites (57–59). It is superior to gas chromatography coupled with mass spectrometry (GC-MS), which needs time-consuming derivatization to become stable, volatile, and amenable to ionization techniques (60). In addition, compared to radioenzymatic methods, the analytical approaches, including extraction techniques and chromatographic conditions, can be adjusted to eliminate potential endogenous or exogenous interferences. Liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) provides a powerful analytical system that allows smaller sample volume and shorter run times, offering increased analytical selectivity and sensitivity because detection is based on retention time, molecular mass, and chemical structure, unique to each molecule (45, 49, 61). LC-MS/MS has become a fundamental tool in next-generation clinical chemistry

and is the gold standard technique for the determination of catecholamines and their metabolites, although the capital costs of the necessary equipment require economic strength of the laboratory (62).

SAMPLING AND STORAGE CONDITIONS

Reference intervals should be established from blood samples collected in supine position under fasting condition and after a period of rest for at least 30 min to reduce the influence of sympathetic activation and upright posture on the release of NE and its metabolism to NMN (42, 63–66). When reference intervals established from supine sampling are used, samples collected under seated condition yield increased rates of false-positive results. Given the extra time and cost of supine sampling, seated sampling has become widespread in most clinical centers (67). In this situation, samples collected in supine position would contribute to false-negative results, with overall decrease in diagnostic sensitivity (from 99 to 96%) (63). Therefore, it is important that sampling for the establishment of reference intervals and sampling for actual diagnosis are performed in the same posture, and the supine position is the best. If this cannot be done, the measurement of urinary fractionated metanephhrines provides an alternative that is not influenced by sampling posture. For storage, in order to preserve urinary catecholamines and their metabolites, the addition of HCl to the urine samples is recommended to maintain a low pH (51). Furthermore, to minimize auto-oxidation and deconjugation, the urine specimens should be kept on ice or refrigerated immediately after collection (68). Catecholamines and VMA in urine are stable at room temperature for only 14 days, while they can be maintained for at least 1 month at 4°C or -80°C (45, 49), the latter ensuring longer storage (51). However, if the samples are assayed within 1 week, urinary fractionated metanephhrines are sufficiently stable at room temperature (69, 70). Blood samples should be collected in tubes containing anticoagulant (heparin or ethylenediamine tetraacetic acid, EDTA), stored at 4°C, and centrifuged within 6 h. Even in the absence of reducing agents, catecholamines are stable in anticoagulated blood for 1 day at 20°C, 2 days at 4°C, 1 month at -20°C, and up to 1 year at -70°C, while plasma free methanephhrines can be kept at 4°C for 3 days without appreciable degradation and stored at -80°C for longer duration (70, 71). Storage conditions should be chosen according to the turnaround time and convenience of the clinical laboratory.

INTERPRETATION OF TEST RESULTS

The correct interpretation of tests is crucial for accurate PPGLs diagnosis. The most common cause of PPGL overdiagnosis is misinterpretation of borderline results (72), while underdiagnosis most commonly reflects failure to consider the importance of test for PPGL. The overdiagnosis might result in unnecessary

adrenalectomy and its complications, and the underdiagnosis might lead to adrenal biopsy with hypertensive crisis and longer hospitalization (72). The interpretation of test results requires an understanding of the metabolism of catecholamines and their physiologic variations. Test results should not be simply labeled normal or abnormal on the basis of reference intervals, but rather should be viewed as a continuum from likely normal to likely indicative of PPGLs.

For plasma free metanephrines or urinary fractionated metanephrines, a four-fold upper limit of reference intervals should be set as a threshold likely indicating PPGL (5). Small PPGLs likely result in slight elevation in levels, between the upper limits and the diagnostic level (32, 73). In such cases, laboratory results, dynamic tests, and additional markers should be carefully evaluated. Because the initial screening of PPGLs crucially depends on biochemical tests subject to occasional laboratory errors, the tests should be repeated to confirm the result (74). In addition, independent makers of neuroendocrine tumors, such as CgA and neuron-specific enolase, should be considered (75–77).

Interferences from medications and diet should be ruled out. Dietary constituents or drugs can either interfere with the *in vitro* assay or alter the levels of catecholamines and their metabolites *in vivo* by affecting the production, release, or metabolism (78). *In vitro* interferences can be avoided by choice of analytical methods, and *in vivo* interferences can be minimized by withdrawing specific dietary constituents or drugs before testing. Caffeine, tobacco, fruits, and nuts can influence catecholamine levels and their metabolism and should be avoided overnight before testing (19). Tricyclic antidepressants, phenoxybenzamine monoamine oxidase inhibitors, and other common medications can cause false-positive elevations (Table 2) (67, 78–83). Notably, L-dopa, used in the treatment of Parkinson's disease, acts as a DA precursor and can cause 3-MT elevations in DA-secreting tumors.

TABLE 2
Medications and diets that may cause false-positive results of catecholamines and their metabolites

Compounds	E	NE	MN	NMN
Drugs				
Phenoxybenzamine	-	++	-	++
Tricyclic antidepressants	-	++	-	++
β-blockers	+	+	+	+
Cocaine	++	++	+	++
Sympathomimetics	+	+	+	+
MAO inhibitors	-	-	++	++
Sulphasalazine	unknown		-	++

Table continued on following page

TABLE 2
Medications and diets that may cause false-positive results of catecholamines and their metabolites (Continued)

Compounds	E	NE	MN	NMN
Levodopa	-	+	+	+
Sotalol	unknown		+	+
Acetaminophen	unknown		-	++
α-Methyldopa	unknown		-	++
Busirone	unknown		++	-
Catecholamines and related drugs	++	++	++	++
Dietary constituents				
Caffeine (coffee, tea)	++	++	unknown	
Nicotine (tobacco)	++	++	unknown	
Theophylline	++	++	unknown	
Alcohol	+	+	unknown	
Catecholamine-rich fruits and nuts	-	+	unknown	

E, epinephrine; MN, metanephrine; NE, norepinephrine; NMN, normetanephrine.

+, mild increase; ++, clear increase; -, little or no increase.

In addition, sampling in seated position can result in elevated metanephries, and this can be easily dealt with by resampling in supine position. If results remain abnormal, normetanephrine levels should be interpreted within the framework of age-adjusted reference intervals and a clonidine suppression test is always helpful (84–86). It is reported that age-adjusted reference intervals minimize false-positives associated with higher normetanephrine plasma concentrations in older patients (87). The clonidine suppression test, based on the principle that clonidine suppresses the normal neurogenically mediated catecholamine release but not that of tumors, can be used to distinguish patients with essential hypertension who have borderline increase in catecholamines and their metabolites from PPGL patients (88). This diagnostic process is illustrated in Figure 2 (17, 31, 89).

Caution should also be taken when evaluating patients with chronic kidney disease, especially if on dialysis, as elevated plasma methanephries are common in this population, even in the absence of PPGL (90, 91). Acute myocardial infarction, hypothyroidism, congestive heart failure, and chronic obstructive pulmonary disease can also result in elevated concentrations of catecholamines (92).

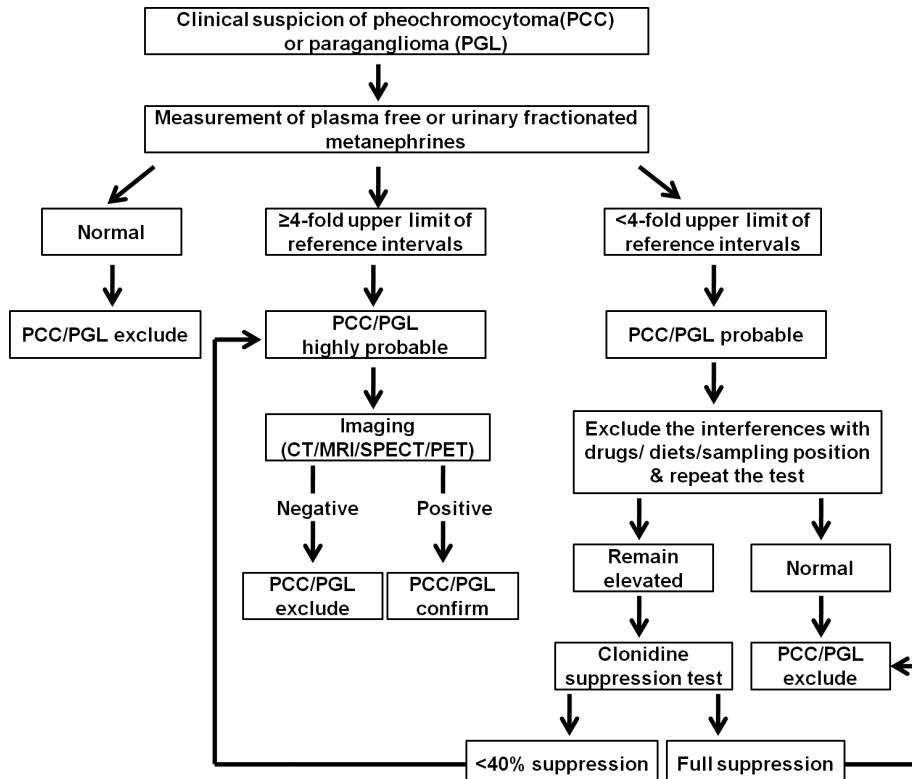


Figure 2 Workflow for the diagnostic evaluation of PPGL patients.

CONCLUSION

PPGL, characterized by overproduction of catecholamines, is potentially fatal, yet usually surgically curable, cause of endocrine hypertension. Improved understanding of catecholamine release and metabolism, and developments in analytical methodologies have made biochemical testing more reliable, efficient, and crucial for the timely diagnosis of PPGL patients. Reference intervals of plasma free metanephhrines are preferentially established using specimens collected via supine fasting sampling, and sampling for actual diagnosis should be performed in the same posture. Although the cutoffs of urinary fractionated metanephhrines are not influenced by sampling, whether plasma free metanephhrines is better than urinary fractionated metanephhrines in terms of diagnostic sensitivity and specificity is a matter of debate; however, plasma sampling is preferable for young persons and outpatients due to its simplicity compared with 24-h urine collection. An increase in plasma free metanephhrines or urinary

fractionated metanephrenes beyond the four-fold upper limit of reference interval indicates that PPGL is highly probable. To interpret borderline results, interferences by drugs, diet, and sampling position should be ruled out. However, the standardization of the biochemical testing methods, sampling, and operational procedures should be urgently promoted in different laboratories for an accurate and timely diagnosis of PPGL.

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