9

Diagnosis: Laboratorial Investigation and Imaging Methods

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1. Introduction

Pheochromocytomas and paragangliomas are rare catechomine-producing tumors. Pheochromocytoma is a chromaffin tumor originating in the adrenal medulla and paraganglioma is originating in the sympathetic and parasympathetic portions of the autonomic nervous system paraganglia. The patients' symptoms are variable according the tumor secretion of norepinephrine (NE), epinephrine (E) or dopamine into the circulation. Patients with tumors predominantly secrete norepinephrine present with severe and refractory hypertension to conventional treatment. Patients with predominantly epinephrine and dopamine-secreting tumors present with episodic symptoms such as tachycardia with palpitations, panic attacks and feelings of doom.

1.1 Multiple Endocrine Neoplasia syndromes (MEN)

MEN 1 is a rare autosomal dominant disease that consists of tumors of the parathyroid glands, pancreatic islets (insulinomas) and anterior pituitary. Pheochromocytoma is not a feature in this syndrome.

MEN 2 is an autosomal dominant syndrome with three recognized sub-types: MEN 2A, B and C. In MEN 2A (Sipple's syndrome), medullary thyroid carcinoma is associated with pheochromocytoma and hyperparathyroidism. Pheochromocytoma is frequently bilateral and the diagnosis is later than medullary carcinoma. Patients who have been treated for medullary carcinoma should be screened for pheochromocytoma.

2. Epidemiology

The prevalence of pheochromocytoma is not precisely known. However, the incidence is about 1-2 per 100,000 adults per year according study in Minnesota (Beard et al., 1983). In countries other than United States, a lesser incidence has been noted about 2 to 8 cases per million inhabitants per year (Stenström & Svärdsudd, 1986). In a large series of patients screened biochemically for suspicion of pheochromocytoma, the incidence has been described to be as high as 1.9%. There was no difference between men and women (Smythe et al., 1992). Recently, a clinical review described the incidence between 2 and 8 cases per million per year in the United States (Golden et al., 2009). In an autopsy series described by McNeil et al. one pheochromocytoma occurred per 2301 autopsies (McNeil et al., 2000). With the routine use of computerized tomography (CT) for abdominal complaints, it is likely that

more tumors will be discovered. The tumor is discovered incidentally in approximately 10% of patients during CT or magnetic resonance imaging (MRI) of the abdomen for unrelated symptoms (Kudva et al., 2003). However, recently others authors reported a 30% rate of incidentally discovered pheochromocytomas in their cohort of patients (Kopetschke et al., 2009; Shen et al., 2010). Pheochromocytoma is present in 0.1% to 1% of patients with hypertension (Omura et al., 2004)

Approximately 10% of adrenal pheochromocytomas and 30% of paragangliomas are considered malignant (Suh et al., 2009). 70% to 80% of pheochromocytomas occur sporadically. The familial syndromes that may present with pheochromocytoma include multiple endocrine neoplasia type 2 (NEM 2), von Hippel-Lindau syndrome, Osler-Weber-Rendu syndrome, and neurofibromatosis syndrome type 1 (Guerrero et al., 2009). The peak incidence occurs in the third to fifth decades of life and the average age at diagnosis is 43.9 years in sporadic cases (Neumann et al., 2002). However, the familial syndromes include younger patients (24.9 years), extra-adrenal and multiple tumors and the hypertension is persistent (Perel et al., 1997). Some authors studied genetic screening in pheochromocytoma and found younger patients with familial syndromes in their cohorts (Manelli et al., 2009; Cascon et al., 2009).

Pheochromocytoma was the most frequent indication for adrenalectomy (23.2%) noted by Villar (Villar et al., 2010).

The 10% rule is no longer applied. The ectopic pheochromocytoma is more prevalent than 10% (Madani et al., 2007). Extra-adrenal tumors are extra-adrenal paragangliomas and the majority is located in the head and neck area (69%), followed by intra-abdominal (22%) and intrathoracic locations (10%) (Van Der Horst-Schrivers et al., 2010). The periaortic, pericaval regions and Zuckerkandl's were the commonest sites of abdominal paragangliomas (Erickson et al., 2001).

3. Pathophysiology

3.1 The sympathetic nervous system (SNS)

The hypertension of pheochromocytoma has been thought to result solely from the action of circulating catecholamines on cardiovascular adrenergic receptors. However, according to the studies of Bravo *et al.*, blood pressure demonstrates no correlation with circulating catecholamines (Bravo et al., 1979). Bravo and collaborators related that sympathetic reflexes are intact, and blood pressure and heart rate are significantly reduced by clonidine despite maintained high circulating catecholamine (Bravo et al., 1982).

In pheochromocytoma patients, the SNS activity is enhanced and maintains the elevated blood pressure by the catecholamine-induced hypertension. The paradoxical elevation of sympathetic activity during elevation of circulating catecholamine is postulated to be due three mechanisms: 1) loading of sympathetic vesicles with catecholamine, presumably reflecting a loading of noradrenergic terminal vesicles with neurotransmitter; 2) increased sympathetic neuronal impulse frequency; and 3) a selective desensitization of presynaptic α_2 –adrenergic receptors. These receptors inhibit release of neuronal NE. Thus, selective desensitization results in enhanced release of neuronal NE during nerve stimulation.

The hypertensive crisis could be produced by any direct or reflexly mediated stimulus to the SNS, because of the enhanced SNS activity and excessive stores of NE in sympathetic nerve terminals (Bravo & Tagle, 2003).

3.2 The neurohumoral agents

Angiotensin II has no direct role in pheochromocytoma, because the administration of clonidine reduces arterial blood pressure without significantly decreasing plasma renin activity (Bravo et al., 1982). Neuropeptide Y (NPY) levels are increased in plasma and in tumors of patients with pheochromocytoma (deS Senanayake et al., 1995; Lundberg et al., 1986). NPY increases coronary and peripheral and vascular resistance independently of α-adrenergic mechanisms by interacting with vascular G protein-coupled receptors (O'Hare & Schwartz, 1989; Lundberg et al., 1982). The hypertensive episodes that occur in pheochromocytoma patients receiving α-blockade might be due the NPY release by the pheochromocytoma.

3.3 Hemodynamic characteristics

Pheochromocytoma patients have hemodynamic features similar to patients with essential hypertension. Thus, increased peripheral vascular resistance seems to be primarily responsible for maintenance of hypertension (Bravo & Tagle, 2003).

4. Diagnosis

Before discussing the role of laboratory diagnosis and research of imaging methods would be interesting to present the patient with symptoms of pheochromocytoma and the reasons would lead to further investigation. The table 1 shows the main points of clinical presentation for screening of pheochromocytoma. In addition, the table 2 shows the main differential diagnosis (Young & Sheps, 2008).

Episodic symptoms of headaches, tachycardia, and diaphoresis
Remember the five "H" characterizing pheochromocytoma: hypertension, hyperglycemia, hypermetabolism, hyperhidrosis and headache
Family history of pheochromocytoma or a MEN syndrome, VHL, or neurofibromatosis type 1
Incidental adrenal or abdominal masses
Unexplained paroxysms of tachyarrhythmias, bradyarrhythmias and /or hypertension during intubation, induction of anesthesia, parturition, or prolonged and unexplained hypotension after an operation
Adverse cardiovascular responses to ingestion, inhalation or injection of certain drugs (anesthetic agents, histamine, glucagons, naloxone, antidopaminergic agents, tricyclic antidepressants)
Attacks occurring during exertion, turning the torso, coitus, or micturition.

Table 1. Patients for screening of pheochromocytoma.

Endocrine
• Thyrotoxicosis
• Primary hypogonadism (e.g, menopausal syndrome)
• Pancreatite tumors (e.g., insulinoma)
• Medullary thyroid carcinoma
• "Hyperadrenergic" spells
Cardiovascular
• Essential hypertension, labile
• Angina and cardiovascular deconditioning
• Pulmonary edema
• Dilated cardiomyopathy
• Syncope
• Orthostatic hypotension
• Paroxysmal cardiac arrhythmia
• Aortic dissection
• Renovascular hypertension
Psychological
• Anxiety and panic attacks
• Somatization disorder
• Hyperventilation
• Factitious (e.g., drugs, Valsalva)
Pharmacologic
• Withdrawal of adrenergic-inhibiting medication (e.g, clonidine)
• Monoamine oxidase inhibitor treatment and concomitante ingestion of tyramine or a decongestant
• Sympathomimetic ingestion
• Ilicit drug ingestion (e.g, cocaine, phencyclidine, lysergic acid)
• Acrodynia (Mercury poisoning)
• Vancomycin (red man syndrome)
Neurologic
• Baroreflex failure
• Postural orthostatic tachycardia syndrome
• Autonomic neuropathy
• Migraine headache
• Diencephalic epilepsy (autonomic seizures)
• Cerebral infarction
• Cerebrovascular insufficiency
Miscellaneous
• Mastocytosis (systemic or activation disorder)
• Carcinoid syndrome
• Recurrent idiopathic anaphylaxis
• Unexplained flushing spells

Table 2. Differential diagnosis of pheochromocytoma.

Approximately 50% of pheochromocytomas produce excessive amounts E and NE and the other 50% predominantely produce NE. Sympathetic paragangliomas produce mainly NE, frequently dopamine, and never E (Eisenhofer et al., 2003).

Measurements of fractionated metanephrines in urine and in plasma or both are the initial testing for pheochromocytoma (Lenders et al., 2002) and no single analysis can achieve 100% accuracy for pheochromocytoma diagnosis.

When the presence of a pheochromocytoma appears likely but with equivocal biochemical testing, a clonidine test is recommended to distinguish true from false positives results (Eisenhofer et al., 2003).

Levels of normetanephrine, metanephrine, or both metabolites are increased in almost all patients with pheochromocytoma. However, in small or microscopic tumors (<1 cm) producing small amounts of catecholamines, the levels of normetanephrine and metanephrine might be normal (Eisenhofer et al., 1999; Lenders et al., 2002). If there is a hereditary predisposition or a previous history for pheochromocytoma, a testing at a later date remains mandatory. False-negative results also could include patients with pheochromocytoma that do not produce NE or E, a more rare exception (Sawka et al., 2003).

4.1 Plasma metanephrines

Normal plasma levels of normetanephrine and metanephrine exclude pheochromocytoma, and no immediate testing for the tumor should be necessary. Thus, measurements of plasma free metanephrines eliminate false-negative in the diagnosis of pheochromocytoma. In contrast, false-positive results remain a common problem, potentially time-consuming and expensive for follow-up. Plasma free metanephrines sensitivity is 99%, followed closely by urinary fractionated metanephrines at 97% (Lenders et al., 2002). The blood sample should be obtained in the supine position. The technique involves the determination of free metanephrines in plasma by high-performance liquid chromatography (HPLC). An elevation of at least four times the upper reference intervals is associated with nearly a 100% probability of pheochromocytoma or sympathetic paraganglioma (Lenders et al., 2005). Elevated catecholamine and metanephrine levels by one to three times the upper limits of normality are usually due to various medications or physiological responses. For tests of plasma free metanephrines the specificity is 89% (Bravo & Tagle, 2003).

False-positive results include medical conditions, medications, inappropriate sampling conditions, and diet. An overnight fast and resting supine before blood sampling minimize the problem. Phenoxybenzamine and tricyclic antidepressants accounted for up to 45% of false-positive elevations of plasma or urinary norepinephrine and normetanephrine (Eisenhofer et al., 2003). However, selective serotonin reuptake inhibitors may provide an alternative medication because they are not a cause of false-positive results.

Phenoxybenzamine is a nonspecific α-adrenoreceptor blocker, causing norepinephrine and normetanephrine elevation by attenuating α_2-adrenoreceptor-mediated feedback inhibition of norepinephrine release, possibly combined with reflexive sympathetic activation. Thus, this drug should be avoided until biochemical testing is complete. Alternative medications for blood pressure control may include calcium channel blockers and selective α_1-adrenoreceptor blockers such as doxazosin and prazosin. Non-selective α-adrenoreceptor blockers were associated with 60% of all false-positive elevations of plasma metanephrine. Nevertheless, the false-positive rate was not high (12.5%). Only if an equivocal result has been obtained, it is necessary repeat testing after withdrawing these medications.

4.2 Urinary free catecholamines and metabolites

Urinary free NE and E and two major metabolites of the catecholamines, metanephrines (normetanephrines and metanephrines) and vanillylmandelic acid (VMA) are relatively easy to perform and are usually readily available. A diagnosis can be confirmed or excluded on the basis of properly collected 24h urine samples (Mannelli, 1989). In MEN syndromes, either 24-h urinary excretion or the calculated ratio of E to NE is a very sensitive screening test (Gagel et al, 1988). The sensitivity of the tests used to detect pheochromocytoma is as follows: urinary NE 86%, urinary E 33%, urinary VMA 64%, plasma NE 58%, and plasma E 33%. Among all tests for pheochromocytoma, the higher specificities are 95 % for test of urinary VMA and 93% for test of urinary total metanephrines (Bravo & Tagle, 2003). The table 3 shows the sensitivity and specificity values of diagnostic tests.

	Sensitivity %		Specificity %	
	Hereditary	Sporadic	Hereditary	Sporadic
Plasma				
Free Metanephrines	97	99	96	82
Catecholamines	69	92	89	72
Urine				
Metanephrines	96	97	82	45
Catecholamines	79	91	96	75
Total Metanephrines	60	88	97	89
Vanilmandelic acid	46	77	99	86

Table 3. The sensitivity and specificity values of diagnostic tests.

4.3 Patterns of biochemical test results

Patients with pheochromocytoma usually have larger relative increases in metanephrines than catecholamines, whereas patients with false-positive results due sympathoadrenal activation usually have larger increases in catecholamines than metanephrines. These differences are possible because pheochromocytoma tumor cells produce metanephrines continuously and release into the circulation independently of variations in release of the parent catecholamines (Eisenhofer et al., 1998).

A plasma normetanephrine to NE ratio above 0.52 or a metanephrine to E ratio above 4.2 can provide confirmatory evidence of pheochromocytoma in up to 30% of patients where increases in plasma metanephrines are insufficient to prove the tumor (Eisenhofer et al., 2003).

4.4 Clonidine-suppression testing

This test was introduced by Bravo *et al.* (Bravo et al., 1981) to distinguish patients with pheochromocytoma from those with false-positive biochemical results. Decreases in elevated NE concentrations after clonidine suggest sympathetic activation, whereas a lack of decrease suggests pheochromocytoma. However, normal suppression occurs and this test is recommended for patients with plasma catecholamine levels over 1000 ng/liter (5.9

nmol/liter), with a normal response defined as a fall to within normal range (Bravo & Gifford, 1984).

Another criterion for a normal response has been a fall in plasma NE after clonidine of more than 50% in patients with normal or only mildly elevated plasma NE levels (Bravo & Tagle, 2003). Plasma normetanephrine is better than NE as end-point marker for the clonidine-supression test, because pheochromocytomas cause larger, more consistent, and less episodic increases of plasma normetanephrine than NE. 76% of plasma normetanephrine is derived from NE released by sympathetic nerves while 90% of circulating metanephrine is normally derived from metabolism of E within adrenal chromaffin cells. Lack of decrease of plasma normetanephrine combined with a high plasma level after clonidine establishes high probability of pheochromocytoma. Plasma normetanephrine concentrations remained elevated after clonidine in 96% of patients with pheochromocytoma compared with only 67% for NE. (Bravo et al., 1981; Eisenhofer et al., 2003).

4.5 Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are sensitive studies and are recommended for initial tumor localization. MRI is preferred for children, pregnant or lactating women, anyone who expresses concern about excessive radiation exposure, and individuals who have had previous surgical resection in abdominal, pelvic, and thoracic cavities. The tumor diameter in majority of pheochromocytomas is greater than 2 cm, thus it is possible diagnose them by CT. The CT sensibility for pheochromocytoma diagnosis is about 90%. However, CT is less sensitive in small tumors. The MRI has a sensibility of 95% for the adrenal tumor bigger than 0.5 cm (Timmers et al., 2009).

Functional imaging agents that target the catecholamine synthesis, storage, and secretion pathways of chromaffin tumor cells are currently used. These techniques include [123/131] metaiodobenzylguanidine (MIBG) scintigraphy, 6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine (DOPA) positron emission tomography (PET), and 6-[^{18}F]fluorodopamine (FDA) PET. Another modality for localization of metastatic paraganglioma is the 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) PET, that is less tissuspecific than the other functional approaches (Timmers et al., 2009).

The ^{123}I-metaiodobenzylguanidine (MIBG) scan has better specificity than CT and MRI, however it is less sensitive in the context of familial paraganglioma syndrome, paragangliomas, and metastatic disease. ^{123}I-MIBG is preferred over ^{131}I-MIBG because of its higher sensitivity, lower radiation exposure, and improved imaging quality with single-photon emission-computed tomography (Timmers et al., 2009). Previous studies suggest a sensitivity of ^{123}I-MIBG scintigraphy of 92-98% for nonmetastatic paraganglioma and 57-79% for metastases (Van Der Horst-Schrivers et al., 2006). Recently a study confirmed that the sensitivity is high for primary tumors and relatively poor (50%) for metastases (Timmers et al., 2009).

Non-metastatic paragangliomas are well localized by these techniques described previously according to Timmers and collaborators (Timmers et al., 2009). However, for the detection of metastases seen on CT, ^{18}F-FDA-PET was superior to ^{18}F-DOPA-PET and ^{123}I-MIBG scanning. ^{18}F-FDG-PET is superior in evaluating metastatic paraganglioma with mutations in succinate dehydrogenase subunit B (SDHB), whereas ^{18}F-DOPA-PET performs best in non-SDHB patients (Timmers et al., 2007). The figure 1 shows the algorithm for biochemical and radiological diagnosis of pheochromocytoma.
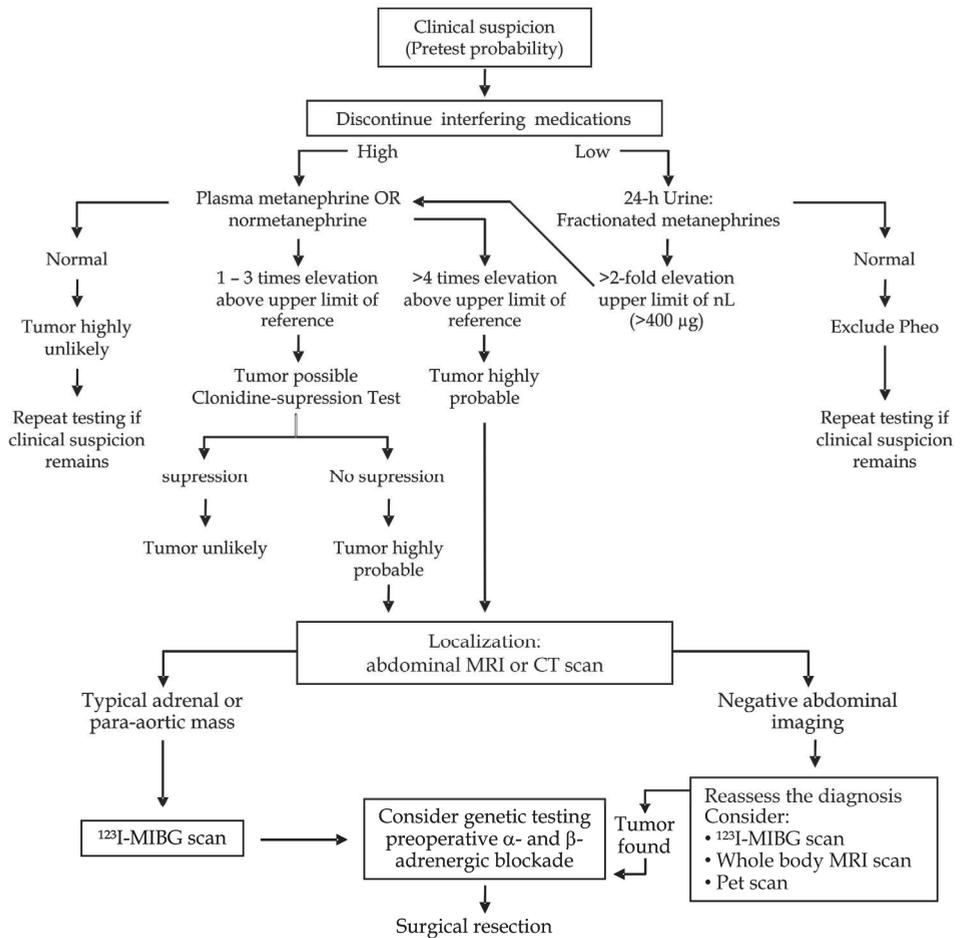
Fig. 1. The algorithm for biochemical and radiological diagnosis of pheochromocytoma.

4.6 Genetics

In actuality, 17 - 35% of pheochromocytomas and paragangliomas have a hereditary background. These hereditary tumors have been described in patients with neurofibromatosis type 1 (NF1), von Hippel Lindau syndrome (VHL), multiple endocrine neoplasia type 2 (MEN 2), and paraganglioma/ pheochromocytoma syndromes types 1-4 (PGL1, PGL2, PGL3, and PGL4) (Gill et al., 2011). The mutated genes are, respectively, NF1, VHL, RET proto-oncogene (Rearranged in Transfection), and subunits of the enzyme succinate dehydrogenase (SDHD, SDH5, SDHC, and SDHB) (Gimenez-Roqueplo et al., 2003). Hereditary pheochromocytomas and paragangliomas can be found at any age. However, most of these tumors are diagnosed in people younger than 50 years of age (Eisenhofer et al., 2011a). The most prevalent among these syndromes is PGL 1, caused

by germline SDHD mutations, followed by PGL 4, whereas PGL 3 is rare (Amar et al., 2005).

The genetic screening should be considered in patients with history for paraganglial tumors, multiple tumors, young age at diagnosis, malignant pheochromocytoma because the prognosis in carriers of SDHB mutations is worse compared with non-SDHB-positive ones (Jiménez et al., 2006). Identification of a patient as a carrier of a germline mutation should be as early as possible. Mutation analysis of NF1 gene is not indicated because patients who have pheochromocytoma and carry this gene mutation also have neurofibromas or other signs of the syndrome. In general, patients presenting with pheochromocytoma who have MEN 2 and a RET mutation will have a personal or family history of MEN 2 features (Eisenhofer et al., 2011b). Mutations of VHL, NF 1 and RET genes are rare. Therefore, mutation analysis of VHL, RET, and NF 1 should not be performed unless there is clear clinical evidence of these syndromic features in the patient and/or family (Neumann & Eng, 2010).

The pathological examination of surgically resected or biopsied tumor tissue or a diagnosis of inoperable malignant pheochromocytoma based on findings of metastatic disease by imaging studies is required to confirm pheochromocytoma.

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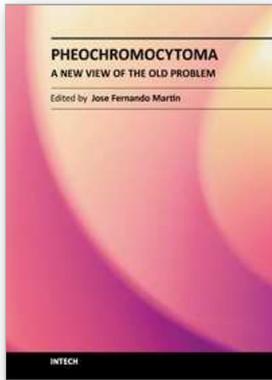
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