Diagnosis of pheochromocytoma with special emphasis on MEN2 syndrome

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ABSTRACT

Pheochromocytomas/paragangliomas (PHEOs/PGLs) are rare but treacherous catecholamine-producing tumors which, if overlooked or improperly treated, will almost invariably prove fatal. Patients with MEN2 PHEOs have a high incidence of paroxysmal attacks and a higher prevalence of hypertension and other cardiovascular problems than do patients with Von-Hippel-Lindau (VHL) PHEOs. Compared to measurements of deconjugated metanephrines, plasma concentrations of free metanephrines are relatively independent of renal function and therefore more suitable for diagnosis of PHEO/PGL. Recently, the focus of Positron Emission Tomography (PET) imaging for these tumors has been the localization of PHEO. Although a limited number of studies are available, [18F]-fluorodopamine ([18F]DA) PET has been found to be the best overall imaging modality in the localization of PHEO. For adrenal PHEOs, this method seems to be comparable to other functional modalities such as [18F]-fluorodopa ([18F]DOPA) PET or [123I]-metaiodobenzylguanidine ([123I]MIBG) scintigraphy. For extraadrenal PHEOs, data are limited and more extensive studies are needed. In patients with metastatic PHEO, the sensitivity of [18F]DA PET is superior to [123I]MIBG. The so called "flip-flop" imaging showing superiority of non-specific [18F] flurodeoxyglucose (FDG) PET over specific [18F]DA PET has been described in rapidly progressive, often metastatic SDHB-associated PHEOs. Whether these data reflect PHEO cell dedifferentiation (e.g. losing Norepinephrine Transporter - NET) or increased metabolic rate remains to be established.

Key words: Multiple endocrine neoplasia, Paraganglioma, Pheochromocytoma, Positron-emission tomography

INTRODUCTION - PATHOGENESIS

Pheochromocytomas (PHEOs) are rare chromaffin-cell catecholamine-producing tumors, primarily located in the adrenal medulla.[1] Extraadrenal chromaffin-cell tumors, known as paragangliomas (PGLs), are usually found along the paravertebral and paraaortic axes.[2] Up to 24% of PHEOs/PGLs are associated with hereditary syndromes: multiple endocrine neoplasia type 2 (MEN2), von Recklinghausen's neurofibromatosis type 1 (NF-1), von Hippel-

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Lindau (VHL) syndrome and familial PGLs caused by germline mutations of the gene encoding succinate dehydrogenase (SDH) subunits B, C and D.[3] Plasma or urine free metanephrines provide biochemical diagnosis of PHEOs/PGLs and tumor localization is obtained with anatomical and functional imaging modalities.[4,5]

Non-functioning PGLs are challenging tumors for clinicians (it should be noted that some are incompletely non-functioning and do secrete moderate amounts of vanillylmandelic acid).[6] They are rare and usually asymptomatic until their size is sufficient to produce symptoms of compression on adjacent organs, especially in cases of abdominal/retroperitoneal tumors.[7]

Up to 36% of PHEOs are malignant.[5] The annual cumulative incidence of PHEOs/PGLs is reported as approximately 3-8 per 10^6 population.[8] Although MEN2-associated PHEOs are usually benign, if left untreated they can be lethal.

GENETICS

In subjects with MEN2 syndrome, activating germline mutations in the RET (REarranged during Transfection) protooncogene (usually in codons 634 or 918; 10q11.2) are found; these mutations are implicated in abnormal cellular proliferation. In patients with MEN2, PHEOs are usually adrenal, benign and bilateral in more than 50% of patients.[9] Children with MEN2B-associated PHEOs have a higher risk of malignancy compared to those with MEN2A or sporadic disease.[10]

EPIDEMIOLOGY

PHEOs manifest in approximately 50% of patients with MEN2A or 2B, most often after the manifestation of medullary thyroid cancer (MTC).[11] MTC occurs rather early in life (in the first and second decades) in patients with MEN2B and follows an aggressive, often lethal course, whereas the average age of diagnosis of MEN2-associated PHEOs is between 30-40 years.[12] Almost all primary PHEOs in patients with MEN2 are localized in the adrenals; less than 5% of these PHEOs are malignant.[11] At diagnosis, 30% of PHEOS in MEN2 are bilateral[13] and in 50% of patients with unilateral disease a second PHEO develops in the contralateral adrenal within ten years.[14]

CLINICAL SYMPTOMS AND SIGNS

The symptoms of PHEOs are variable; overall, tachycardia along with diaphoresis and cephalalgia are encountered in 40%-80% of patients. Although hypertension (either newly diagnosed or exacerbation of known hypertension and most often paroxysmal) is very common (in >90% of all patients with PHEO), this symptom nevertheless remains a non-specific finding.[15]

In contrast to sporadic PHEOs/PGLs, those in familial syndromes, such as in MEN2 and VHL syndrome, exhibit highly distinct gene expression profiles. MEN2 tumors express phenylethanolamine N-methyltransferase (the enzyme that converts norepinephrine to epinephrine), whereas VHL tumors do not; the latter demonstrate activation of hypoxia-angiogenic signaling pathways but also a lower expression of components implicated in catecholamine-related pathways. MEN2 tumors secrete epinephrine or epinephrine and norepinephrine in paroxysmal bursts, while PHEOs in VHL patients show a more sustained catecholamine secretory profile (Table 1).[16] In VHL-related tumors, catecholamine stores are smaller and exhibit a more rapid secretion-dependent turnover compared to MEN2 tumors. The net result is that there are differences in the relative amounts of norepinephrine and epinephrine produced by these two types of tumors; the difference in potency of these catecholamines on alpha and beta adrenoreceptors has been proposed as accounting for the more symptomatic nature of PHEOs/PGLs in MEN2 (in particular for paroxysmal attacks and higher prevalence of hypertension) compared to VHL syndrome.[13,16-18] Signs and symptoms such as palpitations, anxiety, tremor, dyspnea, hyperglycemia and paroxysmal hypertension are more common in patients with tumors that produce epinephrine than in those that do not. Data from our laboratory indicate that these differences are associated with much higher levels of chromogranins A and B and neuropeptide Y in MEN2 than VHL tumors (Table 2).[19,20]

Table 1. Comparison of PHEOs in MEN2 versus VHL

	MEN2	VHL
Tumor localization	Mainly adrenal	Mainly adrenal
Biochemical phenotype	Epinephrine- or epinephrine- and norepinephrine-secreting	Norepinephrine-secreting
Other tumors	MTC, parathyroid hyperplasia	Hemangioblastomas, renal cell carcinoma, pancreatic tumors (possibly neuroendocrine tumors)
Localization modalities	CT or MRI if tumor over 5 cm; perform functional imaging to rule out metastatic disease	Always use functional imaging since NE phenotype suggests that tumor can be located in extraadrenal locations*

*It is very common that in older age adrenal benign adenomas are present

PHEOs: pheochromocytomas, VHL: von Hippel-Lindau, MEN2: multiple endocrine neoplasia type 2, MTC: medullary thyroid cancer, CT: computed tomography, MRI: magnetic resonance imaging, NE: norepinephrine

Table 2. Symptoms of PHEOs/PGLs according to their neuro-secretory products and in particular of Neuropeptide Y (NPY), which is a vasoactive peptide that may contribute to their clinical presentation. Patients with MEN2 or sporadic PHEOs show high levels of NPY compared to VHL-associated tumors (modified/adapted from[3,19])

	High NPY expression		Low NPY expression
	MEN2	Sporadic disease	VHL
Hypertension (%)	42	90	19
Headache (%)	32	92	26
Diaphoresis (%)	32	70	23
Palpitations (%)	37	73	19
Anxiety (%)	21	60	16
Total symptoms (%)	53	90	32

BIOCHEMICAL DIAGNOSIS

PHEOs may secrete catecholamines episodically but they metabolize catecholamines to metanephrines continuously. Plasma concentrations of free metanephrines are relatively independent of renal function and therefore more suitable for diagnosis of PHEO/PGL. The measurement of plasma metanephrines is less cumbersome than determinations in urine and implementation of this test is expanding. Plasma free metanephrines and 24-hour urinary fractionated free metanephrines are accurate, though not infallible, methods for establishing the diagnosis of PHEO/PGL: their sensitivities are 96%-100% and 92%-99%, whereas their specificities are 87%-92% and 64%-72%, respectively.[21-24] Thus, plasma

and urine metanephrines should be considered to be complementary rather than mutually exclusive methods. Normalization of metanephrine levels for populations with normal blood pressure and also for gender and age should be sought,[25] as well as avoidance of interference from medications.[26] We have also found that measurements of plasma free metanephrines not only provide information about the likely presence or absence of a PHEO/PGL but, when a tumor is present, can also help to predict tumor size and location,[26] since biochemical measurements of blood or urine catecholamines are poorly correlated with tumor size, whereas blood or urine metanephrines show strong correlation with tumor size and can be useful in judging the extent and progression of the disease.[4] The PHEOs in MEN2 patients entail a distinct biochemical phenotype in that they consistently produce epinephrine or epinephrine and norepinephrine.

PHEO LOCALIZATION

Anatomical imaging with computed tomography (CT) and/or magnetic resonance imaging (MRI) is used in patients with biochemically-proven PHEOs/PGLs (Table 1). While for most patients imaging is limited to the adrenals/abdomen, imaging of the thorax, neck and head are ordered when malignant/metastatic disease is suspected. PHEOs enhance avidly after contrast medium administration on CT; their contrast washout phase is also prolonged.[27] CT has 93%-100% sensitivity in detecting intraadrenal tumors >0.5 cm.[28] Sensitivity is slightly lower (90%)

for localizing extraadrenal PHEOs >1 cm.[28] MRI is as good as or slightly better than CT for localizing PHEOs; moreover, MRI can detail the relationship of tumors with blood vessels, a feature appreciated when surgery is considered. Although on T2-weighted MRI sequences some adrenal PHEOs show homogeneously high signal intensity, in a recent study most tumors had heterogeneous multiple high intensity areas.[29]

While experience is limited regarding non-functioning PGLs, anatomical imaging cannot reliably differentiate functioning from non-functioning lesions, as is also the case with adrenal tumors;[27] biochemical evaluation—on more than one occasion—is needed to further advance the diagnostic work-up.[30]

There are some caveats in the anatomical imaging for PHEOs/PGLs. False-positive CT/MRI studies can ensue[31] and the specificity of CT/MRI may vary from 50%-90%.[9] In patients with previous surgery, anatomical imaging may not be informative to the clinician, particularly for recurrent, extraadrenal or malignant/metastatic disease.[28] For such patients, functional imaging (implementing nuclear medicine modalities) follows anatomical imaging.

Chromaffin tumors express the human norepinephrine transporter (hNET) and enable the use of specific radiolabeled ligands of molecules that enter the catecholamines' synthesis pathway. Nuclear medicine also makes use of non-specific modalities (since PHEOs/PGLs exhibit high glucose metabolism or express somatostatin receptors).[32] The first choice among nuclear medicine methods is with specific ligands and modalities and, if negative, with nonspecific modalities (particularly if recurrent, metastatic or malignant disease is suspected).

Metaiodobenzylguanidine (MIBG) is a catecholamine precursor that is taken into PHEOs via hNET. It is more commonly labeled with iodine-123 [^{123}I] than iodine-131 [^{131}I]. Sensitivity of [^{123}I]MIBG for PHEOs/PGLs is 63%-100% versus 77%-90% of [^{131}I]MIBG (sensitivity is lower for extraadrenal and/or metastatic disease);[28,33,34] their specificity is 95%-100%.[35,36] MIBG's suboptimal sensitivity is attributed to its low affinity for hNET (the latter's loss possibly resulting from tumor cell dedifferentiation), lack of storage granules, altered vesicle transporter or interference by medications.[37]

Recently, the focus of Positron Emission Tomography (PET) imaging has been the localization of PHEO/PGLs. Although a limited number of studies are available, [^{18}F]-fluorodopamine ([^{18}F]DA) PET has been found to be the best overall imaging modality in the localization of PHEOs.[34] This is more relevant in cases of familial PHEOs, such as in VHL-associated tumors, where functional imaging with [^{18}F]DA PET was demonstrated to be superior to [$^{123/131}$I]MIBG.[37] For adrenal PHEOs, this method seems to be equal to other functional modalities such as [^{18}F]-fluorodopa ([^{18}F]DOPA) PET or [^{123}I]MIBG scintigraphy. For extraadrenal PHEOs, data are limited and more extensive studies are needed. In patients with metastatic PHEO, the sensitivity of [^{18}F]DA PET is superior to that of [^{123}I]MIBG (78% vs 59%).[34] Comparison studies between Octreoscan and [^{18}F]DOPA PET are in progress. The so-called "flip-flop" imaging effect (showing superiority of non-specific [^{18}F]-fluorodeoxyglucose PET over specific [^{18}F]DA PET) has been described in rapidly progressive, often metastatic Succinate Dehydrogenase complex subunit B (SDHB)-associated tumors. Whether these data reflect PHEO cell dedifferentiation (e.g. losing hNET) or increased metabolic rate remains to be established. Functional imaging with [^{18}F]DA PET is useful in the clinical follow-up of patients with familial PHEO: it has proven itself as a useful modality in patients with recurrent disease and experience has shown that it might not be unwise to order functional imaging even in the case of equivocal or slightly positive biochemical findings.[37]

Somatostatin receptors (ST-R) are expressed to some extent by PHEOs/PGLs (mostly types 2, 3 and 5).[34] ST-R scintigraphy (SRS) is useful for localizing malignant/metastatic PHEOs/PGLs with sensitivity approaching 69%-90%.[34,38]

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