DIAGNOSIS, LOCALIZATION AND TREATMENT OF PHEOCHROMOCYTOMA IN MEN 2 SYNDROME

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Pheochromocytomas/paragangliomas (PHEOs/PGLs) in patients with MEN 2 are usually found in the adrenals after the manifestation of medullary thyroid cancer. These PHEOs are commonly bilateral and hormonally active. Tachycardia, diaphoresis and cephalalgia are encountered in 40 %-80 % of patients with PHEOs; hypertension is very prevalent. Plasma concentrations of free metanephrines (or free metanephrines in urine) are best used for the biochemical diagnosis of PHEO/PGL. In patients with biochemically-proven PHEOs/PGLs, anatomical imaging with computed tomography (CT) and/or magnetic resonance imaging (MRI) should be used. False-positive CT/MRI studies can ensue and the specificity of CT/MRI may vary from 50 %-90 %. Functional imaging (implementing nuclear medicine modalities) should follow anatomical imaging; modalities with PHEO/PGL-specific ligands are a first choice. Among these specific modalities positron emission tomography (PET) with [^{18}F]-fluorodopamine ([^{18}F]DA) stands out as the best overall method. If PHEO/PGL-specific modalities turn out to be negative functional imaging should follow with nonspecific modalities (particularly if recurrent, metastatic or malignant disease is suspected). Treatment is surgical, with expanding use of laparoscopic approaches. Overall half of the patients with malignant PHEOs remain alive for 5 years.

Key words: Phaeochormocytoma – MEN 2 – CT – MRI – Diagnosis – Treatment

Up to 24 % of pheochromocytomas (PHEOs)/paragangliomas (PGLs) are associated with hereditary syndromes: von Recklinghausen's neurofibromatosis type 1 (NF-1), von Hippel–Lindau (VHL) syndrome, familial PGLs caused by germline gene mutations encoding succinate dehydrogenase (SDH) subunits B, C and D (PACAK et al. 2007a) and multiple endocrine neoplasia type 2 (MEN 2). In the latter, 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 MEN 2 patients the PHEOs are usually adrenal, benign and bilateral in more than 50 % of patients (MITTENDORF et al. 2007). Not all PHEOs/PGLs are benign and in children with MEN 2B-associated tumors the risk of malignancy is higher compared to those with MEN 2A or sporadic disease (ROSS 2000).

Epidemiology

Medullary thyroid cancer (MTC) usually precedes the manifestation of PHEOs in MEN 2 patients; the latter occur in about half of patients between 30-40 years of age (BRYANT et al. 2003; GIMM et al. 2004). Most primary PHEOs in patients with MEN 2 are localized

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in the adrenals with less than 5 % being malignant (Gimm et al. 2004). One third of PHEOS in MEN 2 are bilateral (Kaltsas et al. 2004) and half of the patients with unilateral disease develop another PHEO in the contralateral adrenal within 10 years.

Symptoms and signs

Tachycardia, diaphoresis and cephalalgia are encountered in 40 %-80 % of patients with PHEOs. Newly diagnosed hypertension (most often paroxysmal) or exacerbation of known hypertension is observed in >90 % of all patients with PHEO (however, this is a non-specific finding) (Kaplan 2006).

The PHEOs in MEN 2 express phenylethanolamine N-methyltransferase (the enzyme that converts norepinephrine to epinephrine) and secrete epinephrine (E) or E and norepinephrine (NE) in paroxysmal bursts (Pacak et al. 2007b). The difference in potency of these catecholamines on alpha- and beta adrenoceptors has been proposed to account for the more symptomatic nature of PHEOs/PGLs in MEN 2 (in particular for paroxysmal attacks and higher prevalence of hypertension) compared to those seen in other familial syndromes, and in particular VHL syndrome (Eisenhofer et al. 2001; Kaltsas et al. 2004; Pacak et al. 2007a; Young 2008). Palpitations, anxiety, tremor, dyspnea, hyperglycemia and paroxysmal hypertension are more common in patients with tumors that produce epinephrine than in those that do not. We have shown that these differences are associated with much higher levels of chromogranins A and B and neuropeptide Y in MEN 2 than VHL tumors (Cleary et al. 2007; Brouwers et al. 2007).

Biochemical diagnosis

Although PHEOs may secrete catecholamines episodically they metabolize catecholamines to metanephrines (metanephrine and normetanephrine; MN & NMN) continuously. Plasma concentrations of free MN & NMN are mostly not influenced by alterations in renal function and are most suitable for diagnosis of PHEO/PGL. The measurement of plasma MN & NMN is less cumbersome than determinations in urine and implementation of this test is expanding. Free MN & NMN in plasma and 24-hour urinary fractionated free MN & NMN are very accurate methods for establishing the diagnosis of PHEO/PGL: sensitivities are 96 %-100 % and 92 %-99 % and specificities are 87 %-92 % and 64 %-72 %, respectively (Raber et al. 2000; Lenders et al. 2002; Sawka et al. 2003; Vaclavik et al. 2007) urine MN & NMN should be best considered to be complementary rather than mutually exclusive methods. However, the normalization of MN & NMN levels for populations with normal blood pressure, as well as for gender and age should be sought (Grossman et al. 2006). Possible interference from medications in the measurement of MN & NMN should be evaluated and avoided (Eisenhofer et al. 2004). We have shown that the measurement of plasma free MN & NMN – in the presence of tumor - can also help to predict tumor size and location (Ilias and Pacak 2004). In MEN 2 the PHEOs are consistently producing either E or E & NE.

PHEO localization

In patients with biochemically-proven PHEOs/PGLs, anatomical imaging with computed tomography (CT) and/or magnetic resonance imaging (MRI) should be used. For most patients the imaging is usually limited to the adrenals/abdomen; views of the thorax, neck and head are ordered when malignant/metastatic disease is suspected. The sensitivity of CT in detecting intraadrenal tumors >0.5 cm is 93 %-100 %, dropping slightly lower (approximately to 90 %) for localizing extraadrenal PHEOs >1 cm (Ilias and Pacak 2004). The experience with MRI shows that for localizing PHEOs it is as good as or slightly better than CT; moreover, MRI can show the relationship of tumors with blood vessels in detail which is greatly appreciated when surgery is considered.

However, we should point to some caveats regarding the anatomical imaging of PHEOs/PGLs: false-positive CT/MRI studies can ensue (Go 1998) and the specificity of CT/MRI may vary from 50 %-90 % (Mittendorf et al. 2007). Furthermore, in patients with previous surgery the anatomical imaging may not be informative to the clinician, particularly either for recurrent, extraadrenal or malignant/metastatic disease (Ilias and Pacak 2004). It is precisely for such patients that functional imaging (implementing nuclear medicine modalities) should follow anatomical imaging.

A particular characteristic of chromaffin tumors is that they express the human norepinephrine transporter [hNET]; this transporter enables the use of specific radiolabeled ligands that enter the catecholamines' synthesis pathway and are used in functional (nuclear medicine) imaging. Other aspects of PHEOs/PGLs such as their enhanced glucose metabolism or expression of somatostatin receptors permit the implementation of

non-specific functional imaging modalities (Shulkin et al. 2006). Functional imaging modalities with PHEO/PGL-specific ligands are a first choice among nuclear medicine methods; if these turn out to be negative functional imaging follows with nonspecific modalities (particularly if recurrent, metastatic or malignant disease is suspected).

PHEOs take up - via hNET - metaiodobenzylguanidine (MIBG), a catecholamine precursor that is nowadays more commonly labeled with iodine-123 [^{123}I] than iodine-131 [^{131}I]. The sensitivity of [^{123}I]MIBG for PHEOs/PGLs is 63 %-100 % versus 77 %-90 % of [^{121}I]MIBG (sensitivity is lower for extra-adrenal and/or metastatic disease) (Ilias and Pacak 2004; Shulkin et al. 2006; Van Der Horst-Schrivers et al. 2006) the specificity of MIBG imaging is 95 %-100 % (Ilias et al. 2003; Cleary and Phillips 2006). The suboptimal sensitivity of MIBG may be attributed to its low affinity for hNET, the latter's loss by tumor cell dedifferentiation, the absence of storage granules, altered vesicle transporters, or interference by medications (Kaji et al. 2007).

Positron emission tomography (PET) imaging has been used to localize PHEO/PGLs for over 10 years. The relevant studies are limited, nevertheless, overall [^{18}F]-fluorodopamine ([^{18}F]DA) PET has been found to be the best overall imaging modality in the localization of PHEOs (Ilias et al. 2008). This is of importance in case of familial PHEOs (such as tumors found in patients with VHL), where functional imaging with [^{18}F]DA PET was shown to be superior to [$^{123/131}$I]MIBG (Kaji et al. 2207). More in detail, 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 extra-adrenal PHEOs, the data are limited and more extensive studies are needed. In studies of patients with metastatic PHEO, the sensitivity of [^{18}F]DA PET was shown to be higher compared to that of [^{123}I]MIBG (78 % vs 59 %) (Ilias et al. 2008). Further studies comparing [^{18}F]DA PET with [^{18}F]DOPA PET and somatostatin receptor (ST-R) scintigraphy are ongoing (see also below regarding the latter). In rapidly progressive, often metastatic tumors the so called "flip-flop" imaging effect is observed (it shows superiority of non-specific [^{18}F]-fluorodeoxyglucose PET over specific [^{18}F]DA PET). It remains to be established whether this effect reflects PHEO cell dedifferentiation (e.g. loss of hNET) or an increase in tumor metabolic rate.

PHEOs/PGLs express - to some extent - mostly type 2, 3 and 5 ST-Rs. The use of ST-R scintigraphy (SRS) is more practical for localizing malignant/metastatic PHEOs/PGLs; sensitivity approaches 69 %-90 % (Ilias et al. 2004; Ilias and Pacak 2008).

Treatment and prognosis

For PHEO/PGL in MEN 2, surgery – whenever possible - is the definitive treatment after preoperative blood pressure lowering/normalization (for tumors that are hormonally active) and should precede thyroid surgery for MTC. Blood pressure is treated with selective alpha-1 blockers (such as prazosin or doxazosin) or nonselective/noncompetitive alpha blockers (such as phenoxybenzamine). Another choice is the use of metyrosine (alpha-methyl-p-tyrosine; an inhibitor of tyrosine hydroxylase that interrupts catecholamine synthesis) in combination with alpha-blockers. Only if blood pressure is treated adequately beta blockers can then be given to treat tachycardia. Preoperative antihypertensive preparation should be instituted at least for 2 weeks before the planned surgery

For most tumors laparoscopic surgery is an option and, depending on surgical experience, cortical- and adrenal vein-sparing adrenalectomy (Brunt et al. 2002). Malignant tumors are better operated transabdominally for debulking. In patients with MEN 2-associated PHEO the risk for eventual bilateral disease, is high. Nevertheless prophylactic contralateral adrenalectomy is not recommended for patients with unilateral tumors (Lairmore et al. 1993).

Inoperable disease is treated with long-acting agents like phenoylbenzamine to control blood pressure or with alpha-methyl-p-tyrosine.

Two to 6 weeks post-surgery biochemical assessment of cure or persistence should be sought with measurement of plasma and/or urine metanephrines. An annual biochemical work-up for the first five years and once every two years thereafter is the minimum required for follow-up.

For persistent/recurrent disease therapeutic [^{131}I] MIBG is an option; one third of tumors show objective response. Chemotherapy (cyclophosphamide, vincristine and dacarbazine) is an option for rapidly progressive metastatic PHEO or for patients with negative MIBG evaluation; in one third of these patients disease remission is observed.

Half of the patients with benign PHEO/PG remain with hypertension although their life expectancy is not considered to be curtailed. Interestingly overall half of the patients with malignant PHEOs remain alive for 5 years after being treatment with various therapeutic modalities.

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