Available online at www.sciencedirect.com
ScienceDirect
Nuclear Medicine and Biology 35 (2008) S1:27–S1:34
NUCLEAR MEDICINE — AND — BIOLOGY
www.elsevier.com/locate/nucmedbio

A clinical overview of pheochromocytomas/paragangliomas and carcinoid tumors☆

Ioannis Ilias[a], Karel Pacak[b,*]

[a]Department of Endocrinology, E. Venizelou Hospital, Athens GR-11521, Greece
[b]Section on Medical Neuroendocrinology, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892-1109, USA

Received 5 March 2008; received in revised form 23 April 2008; accepted 23 April 2008

Abstract

Pheochromocytomas/paragangliomas are rare tumors; most are sporadic. Biochemical proof of disease is better with measurement of plasma metanephrines and less cumbersome than determinations in urine; its implementation is expanding. Anatomical imaging with computed tomography or magnetic resonance imaging should be followed by functional (nuclear medicine) imaging: chromaffin tumor-specific methods are preferred. Treatment is surgical; for nonoperable disease other options are available. Overall 5-year survival is 50%.

Carcinoid tumors derive from serotonin-producing enterochromaffin cells in the fore-, mid- or hindgut. Biochemical screening (and follow-up) is done with measurements of 5-hydroxyindoloacetic acid in urine. For most carcinoids, functional imaging is better than other modalities in localizing primary tumors. Surgery is the treatment of choice; nonresectable tumors are treated with somatostatin analogs or chemotherapy. Overall 5-year survival for patients with carcinoids is 67%.
Published by Elsevier Inc.

Keywords: Pheochromocytomas; Paragangliomas; Radionuclide imaging; Carcinoid tumors

1. Pheochromocytomas/paragangliomas

Chromaffin cells are post-ganglionic sympathetic neurons that produce catecholamines [1]. When fresh tissue samples are oxidized with certain fixatives, their catecholamine content is stained dark grey-brown (*pheos* in Greek). These cells are mainly located in the adrenal medulla; nevertheless, accessory adrenal tissue comprising both cortical and medullary elements has been reported to be particularly localized in the celiac plexus area in 16% of autopsy cases [2]. Tumors arising from extra-adrenal chromaffin cells are termed paragangliomas and they can be found along the paravertebral and paraaortic axes (sympathetic paraganglia have a neck-to-pelvis distribution; parasympathetic paraganglia are found in the neck and skull base) [3]. The paragangliomas that are localized in the adrenal medulla are called pheochromocytomas (or more uncommonly termed adrenal medullary paragangliomas) [4]. Lending itself to some confusion, the term *extra-adrenal pheochromocytomas* is used to describe tumors of the sympathoadrenal system. There are no universally established criteria for defining malignancy in pheochromocytomas/paragangliomas. Capsular invasion and large tumor size (>5 cm in size and >80 g in weight) may be indicators of malignancy; the clinical course may indicate malignancy (particularly with recurrent or metastatic disease).

2. Pheochromocytomas

Pheochromocytomas are rare tumors with an annual incidence of 1–4/10^6 population (Table 1); furthermore, 0.5% of subjects with hypertension and 4% of those with an incidental adrenal mass harbor a pheochromocytoma [5]. Nevertheless, these figures are approximate, since until a few years ago 18–60% of tumors remained undiagnosed during life [4]. The average lag time from the onset of hypertension

☆ This work was supported in part by the Intramural Research Program of the National Institute of Child Health and Human Development. The authors have no conflict of interest to disclose.

* Corresponding author.
E-mail addresses: iiliasmd@yahoo.com (I. Ilias), karel@mail.nih.gov (K. Pacak).

0969-8051/$ – see front matter. Published by Elsevier Inc.
doi:10.1016/j.nucmedbio.2008.04.007

Table 1
An overview of the clinical characteristics of pheochromocytomas/paragangliomas and carcinoids

	Pheochromocytomas/ paragangliomas	Carcinoids
Epidemiology	1–4/10^6	1–2/10^6
Localization	Adrenal and extra-adrenal (mainly torso)	Fore-, mid- and hindgut
Genetics	Mostly sporadic; however, an increasing number of patients (>20%) are currently found to have mutations in *RET, VHL, NF-1, SDHx*	Mostly sporadic; mutations in *MEN1, bcl2*
Products	Catecholamines	Serotonin
Signs	Tachycardia, diaphoresis, hypertension (paroxysmal); pallor	Excess gastrointestinal motility
Symptoms	Cephalalgia, palpitations	Flushing
Anatomical imaging	CT, MRI	CT, MRI
Functional imaging	[^{18}F]DA, [^{18}F]DOPA, [^{123}I]MIBG, SRS	[^{18}F]DOPA, [^{11}C]5-HTP, SRS
Median survival	50%	67%

Please see text for abbreviations.

to the diagnosis of pheochromocytoma is 3 years [6]. Peak age for diagnosis of pheochromocytomas is between 40 and 50 years, with an almost equal female/male ratio. In most cases (downgraded from 90% to 85% or less with the advent of newer molecular genetics studies; see below for details), these tumors are adrenal, sporadic and solitary.

Symptoms of pheochromocytomas vary; the triad of tachycardia with diaphoresis and cephalalgia is encountered in 40–80% of patients and is highly sensitive and specific for a presumptive diagnosis of pheochromocytoma [7,8]. Hypertension (newly diagnosed or exacerbation of known hypertension; most often paroxysmal) is very common (in over 90% of patients) but nonspecific [8].

3. Paragangliomas

Most paragangliomas are intra-abdominal and adjacent to the adrenals (approximately 85%), whereas fewer than 15% are intrathoracic and 1–3% are cervical [9].

Interestingly, neuroendocrine tumor structures in the head and neck regions that are chromaffin negative and related to the parasympathetic nervous system, such as those originating from the carotid bodies or the jugular bulbs, are also termed paragangliomas [10]. These rare tumors usually do not secrete catecholamines (and if they do it is mostly not up to a clinically appreciable level) and follow an indolent no-symptom course as painless neck masses.

4. Genetics of pheochromocytomas/paragangliomas

Familial syndromes with pheochromocytomas/paragangliomas include multiple endocrine neoplasia type 2 (MEN 2), von Hippel–Lindau (VHL) syndrome, neuroectodermal dysplasias [neurofibromatosis type 1 (NF-1), tuberous sclerosis and Sturge–Weber syndrome] and other familial paragangliomas [especially those related to succinate dehydrogenase (*SDH*) gene mutations; see below] [5].

Activating germline mutations in the *RET* (*RE*arranged during *T*ransfection) protooncogene (usually in codon 634 or 918; 10q11.2) are implicated in the abnormal cellular proliferation of the MEN 2 syndrome. Pheochromocytomas are usually adrenal and benign in MEN 2 and bilateral in more than 50% of patients [5].

Commonly missense mutations in the *VHL* tumor suppressor gene (usually in codon 167; 3p25–26) are implicated in the pathogenesis of VHL syndrome, with 25–50% of subjects having mostly benign pheochromocytomas (and slightly less than 50% with bilateral disease) [5].

The genetic background of pheochromocytomas observed in subjects with neuroectodermal dysplasias is yet to be elucidated, although mutations in the *NF-1* tumor suppressor gene — associated with von Recklinghausen's disease — have been observed (17q11.2; in 90% of cases). The risk of pheochromocytoma in patients with NF-1 is approximately 1–5% [6,11].

Familial pheochromocytomas or head/neck paragangliomas are seen in subjects with germline mutations in Subunits B, C and D of the *SDH* gene; the risk of extra-adrenal and/or malignant disease is high for *SDHB* mutation carriers [5,12,13].

The current paradigm of pheochromocytomas being "10% tumors," i.e., 10% extra-adrenal, 10% malignant or 10% hereditary, is in flux, since mutations in the *SDHB, SDHD, VHL* or *RET* genes have been identified in 12–25% of patients with apparently sporadic pheochromocytomas [14,15]. Consequently, in patients (currently mainly of age 50 or younger) with apparently sporadic pheochromocytomas and their kin, mutation screening is advised [6,16].

5. Biochemical diagnosis

Hormonally active chromaffin tumors may secrete catecholamines episodically, but they metabolize catecholamines to metanephrines continuously (Fig. 1). Free metanephrines in plasma and 24-h urinary fractionated free metanephrines are accurate — but not infallible — methods for establishing the diagnosis of pheochromocytoma. Their respective sensitivity ranges from 96% to 100% and 92% to 99%, and their specificity is 87% to 92% and 64% to 72% [17–20]. The measurement of plasma metanephrines is less cumbersome than determinations in urine, and its implementation is expanding. Urine and plasma measurement of metanephrines should be considered as being complementary rather than mutually exclusive methods. Care to normalize metanephrine levels for populations with normal blood pressure, as well as for gender and age, must be taken [21]. In any biochemical evaluation for pheochromocytoma/