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Subclinical Phaeochromocytoma

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Abstract

Phaeochromocytomas and paragangliomas are neural crest-derived tumours. Autopsy studies indicate that relatively large numbers of these tumours remain undiagnosed during life. This may reflect non-specific signs and symptoms and low medical alertness in evaluating the clinical picture or it may reflect a silent clinical presentation - the subclinical phaeochromocytoma. The associated clinical picture depends on the capacity of the tumours to release catecholamines and sometimes biologically active peptides. Hypertension is the hallmark of catecholamine release, but the amount, type and pattern of catecholamine secretion is extremely variable. Some tumours have low or intermittent secretory activity, some produce mainly or solely dopamine, while others very rarely do not synthesize or release any catecholamines (non-secretory or non-functional tumours). Such tumours may present with mild or even absent signs and symptoms of catecholamine excess. Low secretory activity may reflect small tumour size or differences in secretory phenotypes associated with the biochemical and genetic background of the tumours. Tumours due to succinate dehydrogenase subunit B mutations are often subclinical, poorly differentiated, contain low amounts of catecholamines, and are usually malignant at diagnosis. Adrenoceptor desensitization can result in a subclinical presentation, even when catecholamine levels are high. Subclinical phaeochromocytomas are often discovered as incidentalomas during radiological procedures or during routine screening for phaeochromocytoma in carriers of mutations in one of the ten currently identified tumour susceptibility genes. Undiagnosed phaeochromocytomas, whether or not subclinical and even if biologically benign, may cause extremely deleterious consequences or even death, following abrupt release of catecholamines.

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Keywords

Phaeochromocytoma; paraganglioma; subclinical; catecholamines; incidentalomas; malignant; susceptibility genes

Introduction

Phaeochromocytoma (Phaeo) is a neuroendocrine catecholamine releasing tumour arising from the chromaffin cells in the adrenal medulla (1). When arising outside the adrenal gland, the tumour is referred to as a secreting paraganglioma (sPGL) (2-4), which should be distinguished from other paragangliomas, located in the head and neck region (HNPGL). In contrast to Phaeos and sPGL, which are sympathetic in origin and almost always produce catecholamines, HNPGLs are parasympathetic in origin and generally do not produce significant amounts of catecholamines (5, 6) (table 1). Therefore, signs and symptoms of HNPGLs are local and linked to their size (7, 8). When sufficiently enlarged, they can cause compression of adjacent tissues and nerves or appear as a neck nodule. Often they are incidentally discovered during sonography of thyroid or carotid arteries.

In contrast to HNPGLs, the clinical presentation of Phaeo/sPGL depends mostly on their capacity to synthesize and release catecholamines (noradrenaline, adrenaline and dopamine) with signs and symptoms principally linked to ensuing adrenergic receptor stimulation. The clinical picture of these tumours is extremely variable (9-13) reflecting heterogeneity among tumours and the amount, type and the pattern of catecholamine secretion.

Autopsy studies have indicated that a significant proportion of Pheo/sPGL remain undiagnosed during life. The literature is also rich with case reports showing the dramatic consequences of undiagnosed Phaeo/sPGL. Before 1962, 53% of these tumours were reported to go undiagnosed before surgery or autopsy (14, 15). After the advent of imaging techniques such as sonography, computed tomography (CT) and magnetic resonance imaging (MRI), this percentage has certainly dropped; in fact, at present, a consistent percentage of phaeo/sPGL are detected as incidental masses, mostly in the adrenals (adrenal incidentalomas) (16, 17). Nevertheless, large proportions of these tumours remain undiagnosed or are diagnosed at a late stage after occurrence of cardiovascular complications.

What are the reasons for missing a diagnosis of Phaeo/sPGL? One reason is that none of the signs or symptoms (1, 9) (table 2), alone or grouped, are sufficiently sensitive or specific to allow firm diagnosis simply on clinical grounds. The signs and symptoms are common to many other pathological conditions (2) (table 3). This makes the diagnosis of Phaeo/sPGL, also referred to as “the great mimic”, a real challenge, especially for clinicians with a low level of medical alertness.

A second reason is that some Phaeo/sPGL present with a silent clinical picture. Here these tumours are referred to using the term “subclinical phaeochromocytoma”. In medicine the term “subclinical” generally refers to a disease that is not severe enough to present with definite or readily observable symptoms. This condition is present when a disease is not severe enough either as a chronic condition or as a stage in a disease before the symptoms are first noted. For endocrine diseases, the term is generally used to refer to conditions of very mild derangements of hormone secretion. This statement is not fully applicable to Phaeo/sPGL where a subclinical presentation may depend not only on the amount but also on the type of secretory products released. Moreover, reflecting variability in secretory

patterns, the subclinical condition may be present only occasionally or transitorily in the course of the disease.

In the literature Phaeo/sPGL with a mild or silent clinical presentation have been variously termed as asymptomatic (18, 19), unsuspected (14, 15), non-functioning (20, 21) or non-secreting (22). In this article we discuss the factors responsible for subclinical presentations of Phaeo,/sPGL, the conditions when a subclinical Phaeo/sPGL can be found and the consequences which may derive from an undiagnosed subclinical Phaeo/sPGL.

Tumour characteristics influencing the clinical picture

Size

No solid data are available on the growth rates of Phaeo/sPGL, but the amount of catecholamines and metanephrines released by the tumour are in general positively correlated with tumour size (23). Therefore, small Phaeo/sPGL in their early stages of development are generally associated with few or mild symptoms.

Phaeo/sPGL are highly vascularised tumours, often presenting with haemorrhagic areas (17, 24). Therefore, also large Phaeo/sPGL with extensive internal necrotic/haemorrhagic areas may be associated with a mild clinical picture. In some patients, an extensive intratumoural haemorrhage may cause an acute hypertensive emergency followed by a temporary disappearance of symptoms, which makes the clinical picture even more misleading. Rarely, large tumours may be asymptomatic even in the absence of intra-tumoural necrosis. Such tumours, which have been reported in patients with succinate dehydrogenase subunit B *(SDHB)* mutations (25), have an undifferentiated catecholamine biosynthetic phenotype, contain low or negligible concentrations of catecholamines and can reach large sizes before secreting sufficient amounts of catecholamines to produce signs and symptoms; in some, their presence only becomes apparent due to the space-occupying complications of the mass.

Type and pattern of catecholamine release

The clinical presentation of Phaeo/sPGL mostly depends on the type and pattern of catecholamine release. Phaeo/sPGL can be broadly distinguished with either noradrenergic or adrenergic phenotypes (26). Production of adrenaline defining the adrenergic phenotype depends on tumour expression and activity of phenylethanolamine-N-methyltransferase (PNMT), the enzyme that converts noradrenaline to adrenaline. Such tumours contain and secrete both noradrenaline and adrenaline in various proportions. Tumours lacking PNMT activity do not produce significant amounts of adrenaline and are typically characterized by a noradrenergic phenotype (27). These two phenotypes are found in groups of both sporadic tumours and tumours (28) resulting from a germ-line mutation in one of the currently identified 10 Phaeo/sPGL susceptibility genes: *VHL* (29), *RET* (30), *NF1* (31), *SDHA* (32), *SDHB* (33), *SDHC* (34), *SDHD* (35), *SDHAF2* (36), *TMEM127* (37), and *MAX* (38).

Gene mutation determines tumour catecholamine phenotype (39). Tumours due to *RET*, *NF1* and *TMEM127*-mutations have an adrenergic phenotype (26, 40), while those due to *VHL* mutations have a noradrenergic phenotype (26).

The two main types of adrenergic and noradrenergic tumours are also characterised by differences in their patterns of catecholamine secretion and expression profiles of components of the secretory machinery. MEN2 and NF1 tumours have higher intratumoural catecholamine concentrations, lower plasma concentrations of catecholamines relative to tumour size and display a more mature regulated secretory pathway in comparison to VHL tumours (26).

The clinical consequences of the above biological differences are that Phaeo/sPGL in MEN 2 patients do not release catecholamines as readily or as continuously as those in VHL patients. Nevertheless, the former tumours can be more easily provoked by secretagogues to release their catecholamines. Thus, patients with adrenaline-secreting tumours present more often with paroxysmal signs and symptoms, but outside the secretory crisis the patient can present with normotension and clinical silence. On the other hand, in patients with predominantly noradrenaline-secreting tumours the clinical picture can be mild, generally characterized by blood pressure values resembling essential hypertension. Moreover, in some of these patients, the continuously higher plasma concentrations of noradrenaline may induce a down-regulation of adrenoceptors (41, 42), which thus contributes to an even milder clinical picture, sometimes to a normal blood pressure profile.

Dopamine (DA)-producing Phaeo/sPGL are rare (43), but reasonably common among patients with SDHB and SDHD mutations. Such tumours most usually co-release noradrenaline. Those producing exclusively DA are extremely rare and caused by a lack of tumoural expression of DA-β-hydroxylase, the enzyme that converts DA to noradrenaline (44). Tumoural production of DA can be documented by measuring DA in the plasma or its O-methylated metabolite, 3-methoxytyramine, in plasma or urine (45). Urinary DA reflects DA synthesized in the renal tubules and its measurement has limited clinical relevance in the diagnosis of Phaeo/sPGL.

DA release from a Phaeo/sPGL indicates a more immature tumour and in fact malignant Phaeo/sPGL are frequently DA-releasing. An increase in 3-methoxytyramine levels should be considered a risk factor for malignancy (46).

Increased DA plasma levels have cardiovascular consequences (47) as DA may act on peripheral DA type 1 receptors causing vasodilation and on peripheral presynaptic DA type 2 receptors (48) causing a decrease of noradrenaline release from sympathetic nerve endings (49, 50). Both these effects may counteract vasoconstriction and any cardiac action caused by noradrenaline co-released by the tumour, thus attenuating the clinical picture.

The vast majority of PGLs that do not produce or secrete catecholamines, as reported above, are generally parasympathetic in origin and located in the head and neck region (HNPGL) or in the upper/anterior mediastinum (5). Non-secreting or non-functional abdominal Phaeo/PGL due to similar lack of catecholamine synthesis are very rare, sometimes associated to *SDHB* mutations. In theory, lack of catecholamine release might be present in Phaeo/PGL that do not secrete catecholamines but metabolize them to inactive compounds or in tumors that do not even synthesize or contain catecholamines as a result of a defect in tyrosine-hydroxylase, the key enzyme in catecholamine synthesis. In the literature, only rarely the lack of catecholamine release and its causes have been convincingly documented (22). Obviously, these tumours are clinically silent and incidentally discovered at radiology or at autopsy or, when malignant, they may present with symptoms of metastatic disease.

Co-secreted peptides (table 4)

some of the peptides possibly co-released with catecholamines by the tumour (51), such as adrenomedullin (52), and PACAP (pituitary adenilate-cyclase activating peptide) (53) may have vasodilating effects. Depending on the amount of these peptides released, the clinical picture may be influenced through a counteracting of some of the effects exerted by the catecholamines.

Clinical settings with a subclinical Phaeo/sPGL

Incidentalomas

In autopsy studies, the mean prevalence of adrenal masses was found to be approximately 6% (54). This finding seems to be confirmed by the 4% prevalence of adrenal masses detected at CT (55). Human adrenals have been shown to develop adrenal nodules with increasing age, so that after 70 years the probability of developing an adrenal nodule is about 7%. Phaeo has been demonstrated to account for more than 4% of all adrenal masses in a large series of patients presenting with an adrenal incidentaloma (16). In a retrospective study conducted on 298 Italian patients affected by Phaeo/sPGL, 11.2% of the tumours were incidentally diagnosed, and among these, 62.5% were normotensive (9).

Some radiological characteristics can suggest the chromaffin nature of an incidentaloma due to the high vascularisation of Phaeo/sPGL and the frequent presence of intratumoural haemorrhages. These characteristics account for their typical high signal on T2-weighted imaging and strong enhancement after contrast agent administration (17). Although suggestive, these findings do not allow the diagnosis, which has to be confirmed by laboratory results.

In view of the potential dangerous consequences related to an undiagnosed Phaeo/sPGL, it is the authors' opinions that measurement of plasma or urinary metanephrines (56) is recommended in each patient affected by an adrenal incidentaloma and is mandatory in every patient scheduled for surgery of an adrenal incidentaloma.

Genetic screening

To date, 10 susceptibility genes have been discovered (29-38) and the average percentage of the familial cases is around 40% (57, 58). The proportion increases with decreasing ages of patients, but there remains no formal agreement on age-related cut-offs under which genetic testing is recommended. Genetic testing is nevertheless important (57, 59, 60) either for the patient, indicating the risk of developing multiple Phaeos/PGL or harbouring associated syndromic lesions, as well as for the family members affected by the gene mutation. Each carrier should be enrolled in a follow-up program aimed at an early diagnosis. For Phaeos/sPGL, measurement of plasma or urinary metanephrines is generally recommended about once a year. For patients with *SDHB* and *SDHD* mutations, screening should include additional measurements of plasma or urinary methoxytyramine. Plasma chromogranin A measurement might also be useful in the screening and follow up of *SDHB* mutation carriers. A regular follow-up will permit a diagnosis of phaeo/sPGL at an early stage when the tumour is still small and the clinical picture is mild or even silent. It is likely that, due to the screening of carriers, subclinical Phaeo/sPGL in the future be detected in increasing numbers of patients.

Consequences of undiagnosed subclinical Phaeo/sPGL

Phaeo/sPGL are generally benign tumours, but may be "malignant" on clinical grounds because of the metabolic (12) and cardiovascular effects (61) exerted by the high levels of circulating catecholamines. The most deleterious consequences are caused by the abrupt release of catecholamines, which may occur spontaneously or may be caused by a large series of different factors (Table 5).

A subclinical picture does not exclude the potential occurrence of hypertensive crises (62, 63) causing serious cardiovascular events and even the death of the patient. The literature is rich with case reports showing the dramatic consequences of undiagnosed Phaeo/sPGLs and as suggested by the various autopsy studies (15, 64, 65), most of these undiagnosed tumours

presumably contribute to premature death. A very high medical alertness is therefore recommended when even mild signs or symptoms suggest possible presence of these tumours (66).

Summary

Phaeo/sPGL present with an extremely variable clinical picture which ranges from dramatic, to mild, to silent, depending on tumour attitude to release catecholamines. Hypertension is the hallmark of these tumours but is not always present. Subclinical Phaeo/sPGL are incidentally discovered during radiological procedures or screening of family members resulted carrier of a mutation in one of the so far known susceptibility genes. A subclinical picture may depend on several factors such as tumour size, type and amount of catecholamines released, sensitivity of peripheral adrenoceptors. Malignant Phaeo/sPGL, frequently associated to *SDHB* mutations, often display a subclinical picture, being less differentiated and often dopamine-secreting. Subclinical Phaeo/sPGL should never be considered safer than those with an overt clinical presentation as a sudden hypertensive crisis, due to an abrupt spontaneous or provoked catecholamine release, is possible.

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Table 1

Nosology of Phaeochromocytomas/Paragangliomas

Name	Location	Secretion	Origin	Definition
Phaeochromocytoma	Adrenal gland	catecholamines	Sympathetic	phaeochromocytoma
Paraganglioma	Extra-adrenal Abdomen, Thorax	catecholamines	Sympathetic	sPGL (secreting paraganglioma)
Paraganglioma	Head/Neck Carotid body, vagal, jugular, tympanic, laryngeal glomus	Absent (DOPA, Dopamine)	Parasympathetic	HNPGL (Head-Neck paraganglioma)

Table 2

Signs and Symptoms referred by patients with chromaffin tumours and their approximative frequencies

Signs and Symptoms	Frequency
Headache	60-80%
Tachycardia/Palpitations	50-70%
Sweating	40-60%
Anxiety	20-40%
Sustained hypertension	50-60%
Paroxysmal hypertension	40-60%
Pallor	35-45%
Nausea	20-25%
Weight loss	20-40%
Orthostatic hypotension	10-20%
Glucose Intolerance/Diabetes	40-50%
Flushing	10-20%
Dyspnea	10-20%
Vertigo	10-20%

Table 3

Pathological conditions mimicking chromaffin tumours

Hyperthyroidism
Hypoglycemia
Medullary thyroid carcinoma
Mastocytosis
Menopausal syndrome
Panic disorder
Migraine
Carcinoid syndrome
Ischemic heart disease
Heart failure
Stroke
Arrhythmias
Epilepsia
Migraine
Drugs (monoamino-oxidase inhibitors, sympathomimetics, clonidine withdrawal, cocaine)

Table 4

Peptides possibly secreted by chromaffin tumours

Peptide	Correlated Signs/ Symptoms
VIP (vasointestinal peptide)	Diarrhea, flushes
Substance P	Flushes
Somatostatine	Constipation
Enkefaline	Constipation
Motiline	Diarrhea
Neuropeptide Y	Vasoconstriction
Renin	Hypertension
CRF (Corticotrophin Relising Factor)	Hypercortisolism
ACTH (Corticotrophic Hormone)	Hypercortisolism
MSH (Melanocyte stimulating hormone)	Melanodermia
PTH (Parathyroid Hormone)	Hypercalcemia
PTHRP (PTH-related Peptide)	Hypercalcemia
Endothelin	Vasoconstriction
Erythropoietin	Polycythemia
ACE (Angiotensin converting enzyme)	Hypertension
GHRH (Growth Hormone Relising Hormone)	Acromegaly
IL-6 (interleukin 6)	Fever
NSE (Neuron Specific Enolase)	
ANP (Atrial Natriuretic Peptide)	Polyuria, hypotension
IGF-II (Insulin-like Growth Factor II)	
Chromogranin A	
Calcitonin	
CGRP (Calcitonin-related peptide)	Vasodilation
PACAP (Pituitary adenylate-cyclase activating peptide)	Vasodilation
Adrenomedullin	Vasodilation

Table 5

Factors reported to induce hypertensive crises in patients with phaeochromocytoma

Mechanical: palpation of abdomen, physical exercise, change of posture, cough or sneezing, defecation, sexual intercourse, delivery, surgery, invasive diagnostic procedures (venous sampling, arteriography, fine needle biopsy), micturation (in cases of bladder sPGLs)
Drugs: Histamine, tyramine, glucagon, alcohol, nicotine, sympathetic amines, metoclopramide, chlorpromazine, tricyclic antidepressants, monoamine oxidase inhibitors, steroids, non-cardiac selective beta adrenergic receptor blockers, naloxone, saralazin, theophylline, caffeine, chemotherapeutic agents, neuromuscular blocking agents.
Others: pain, emotional stress, cold exposure.