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Clinical evaluation and treatment of phaeochromocytoma

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Abstract

Phaeochromocytoma and extra adrenal paraganglioma are rare neuroendocrine tumours and have the potential to secrete adrenaline, noradrenaline and dopamine causing a myriad of clinical symptoms. Prompt diagnosis is essential for clinicians and requires a multidisciplinary specialist approach for the clinical and laboratory investigation, diagnosis, treatment and follow-up of patients. This paper is an integrated review of the clinical and laboratory evaluation and treatment of patients suspected to have phaeochromocytoma or paraganglioma, highlighting recent developments and best practices from recent published clinical guidelines.

Introduction

Phaeochromocytomas are rare neuroendocrine tumours that arise from sympathetic adrenomedullary chromaffin tissue.[1,2] These tumours usually produce one or more catecholamines: noradrenaline (NAd), adrenaline (Ad) and dopamine (DP). In contrast, paragangliomas are derived from extra-adrenal chromaffin tissue of the paravertebral ganglia of abdomen, pelvis and thorax. Differences in clinical features and behaviour suggest that they should be regarded as different diseases.[3]

Paragangliomas do not typically secrete Ad due to the reduced expression peripherally of the cortisol-dependant enzyme phenylethanolamine-N-methyltransferase, which converts NAd to Ad.[4]

Paragangliomas can also arise from parasympathetic ganglia found along the glossopharyngeal and vagal nerves in the neck, and base of the skull.[2] The latter are usually biochemically silent.

Phaeochromocytomas account for approximately 85%, and sympathetic and parasympathetic paragangliomas 15–20%, of chromaffin cell tumours.[5] For simplicity, throughout this article phaeochromocytomas and paragangliomas will be referred to as PPGL.

The prevalence of PPGL varies according to the population studied. In an outpatient hypertensive population, the prevalence is reported as 0.2–0.6%.[6–9] Autopsy studies show that 0.05–0.1% of patients have undiagnosed tumours.[10–12] It has been suggested that the prevalence of the latter is falling as more PPGL are

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being picked up, while people are alive owing to better screening tests and more incidental findings during imaging for other reasons. It is estimated that 1.5–14.0% of incidentally discovered adrenal masses found on computerized tomography (CT) or magnetic resonance imaging (MRI) are phaeochromocytomas.[13–15]

The most common indications for biochemical screening for PPGL are: (a) the presence of both hypertension and episodic symptoms of catecholamine excess (e.g. palpitations, headache and periods of diaphoresis); (b) treatment of resistant hypertension; (c) assessment of functionality of incidentally identified adrenal masses; (d) predisposition to hereditary PPGL and (e) assessment of recurrence of PPGL.

Clinical presentation

PPGL are notoriously difficult to diagnose, especially for the non-specialist clinician as they are rare in the community. Most clinicians never see a patient with a PPGL, and the symptoms can be mixed and if not clearly analysed are similar to those of many diseases, including anxiety attacks. Moreover, unless the diagnosis is considered, it cannot be reached. Symptoms vary according to which catecholamine is being secreted, and therefore which α- and/or β-receptor(s) are being stimulated. Only 30–40% of patients demonstrate the classic triad of headache, palpitations and diaphoresis associated with functional PPGL.[16,17] In many patients, hypertension will be associated with these symptoms. Patients may have been diagnosed with hypertension previously and treated with polypharmacy due to the resistance of the hypertension. This group of patients along with young hypertensive patients (<40 years old) should be screened for causes of secondary hypertension, including PPGL. Catecholamine secretion can be episodic or continuous; this variable symptomatology contributes to the difficulty in making the diagnosis.

Resistant or labile hypertension

Hypertension is present in 70–80% of patients with PPGL.[16,17] It may be described as labile or paroxysmal (37%) but is often persistent hypertension (63%).[17] Persistent hypertension is more usual with a predominant NAd-producing tumour, whereas Ad is associated with orthostatic and paroxysmal hypertension.[18] Labile hypertension can cause difficulties in treatment, resulting in the trial of many different antihypertensive drugs at different dosages. This trial of different agents without success should raise the suspicion of the potential presence of PPGL. When hypertension appears resistant to single therapy, one should be suspicious of a possible PPGL. This tends to be more prevalent in the young hypertensive population, and while PPGL

only accounts for a small percentage (2–4%) of these patients,[19,20] it is curable and so should be screened for.

Normotensive patients

Although frequently associated with hypertension, 5–55% of patients will be normotensive.[16,17,21] Due to this, they may be incidentally discovered or go undiagnosed without the paroxysmal nature of the hypertension or the presence of orthostatic hypotension on standing. Lower concentrations of catecholamines may be seen more in normotensive PPGL patients than in those who are hypertensive. While it makes sense that the extent of symptoms is related to the concentration of catecholamines produced, this does not necessarily correspond to size of the tumour on imaging.[17]

Palpitations/cardiac events

Palpitations (runs of tachycardia sometimes associated with anxiety but, in the absence of a causative stressful event) may result from PPGL. In such situations, the symptoms may be mistakenly attributed to anxiety[22] or a stress response provoked by a particular event. Palpitations usually result from the stimulus of β1-receptors. PPGL can also present with cardiomyopathies, pulmonary oedema and cardiac arrests.[23]

Sweating and pallor

Stimulation of the α1-receptor causes sweating and is seen in a number of patients with PPGL.

A typical loss of colour or pallor is seen in PPGL patients, where they are described as going 'white' due to vasoconstriction caused by α1-receptor stimulation. Vasoconstriction can also be peripheral. This can be observed when the α1-receptors are blocked in preparation for surgery, when often there is a visible change in skin colour and temperature.

Headache

Headaches are often precipitated by the increase in blood pressure and vasodilation and are more common in hypertensive PPGL patients than in normotensive patients.[17]

Abdominal pain

Abdominal pain can be an associated symptom of PPGL in a stressful event, precipitating an acute crisis.[24]

Hyperglycaemia

Diabetic ketoacidosis, type 2 diabetes and hyperglycaemic crisis have been reported as a presenting feature

of PPGL, especially when there are atypical features such as labile hypertension or a patient's failure to respond to insulin therapy.[25,26]

Catecholamines normally prevent hypoglycaemia by promoting lipolysis, gluconeogenesis and glycogenolysis through stimulation of β_2-receptors and are a cause of insulin resistance. The excess uncontrolled secretion of catecholamines from a PPGL can therefore result in hyperglycaemia. Elective surgical treatment can lead to a reduction in dose of diabetic medication or even cure the patient's 'diabetes'.[27]

Unusual symptoms

As there are numerous effects resulting from α- and β-receptor stimulation, PPGL can less commonly present with symptoms including hypercalcaemia and hypercortisolaemia[28] due to the increased secretion of ACTH and thromboembolic events.[29,30]

Phaeochromocytoma crisis

PPGL crisis is defined as an acute severe presentation of a catecholamine-induced haemodynamic instability causing end-organ damage or dysfunction.[31] It can be divided into types A and B. Type A represents a limited crisis with haemodynamic instability and end-organ dysfunction or damage of one or more organs. Type A can progress to type B, which is an extensive crisis with the patient going into shock. Type B crisis is characterized by sustained hypotension and multiorgan damage of two or more systems.[32] This diagnosis can be confused with myocardial infarction, septic shock and cardiomyopathy.[30]

A crisis can be precipitated by many factors including a general anaesthetic in an unprepared patient, direct trauma to the tumour, drugs including metaclopramide and some contrast agents. Type A crisis carries a 6% mortality, while type B confers a higher mortality of 28%.[32]

Investigation

Biochemical screening

Recent clinical practice guidelines[1] for the diagnosis of PPGL state that total fractionated urine metadrenalines (UMets) or plasma-free metadrenalines (PMets) should be used as an initial biochemical screen for PPGL. The purported advantages and disadvantages of plasma and urine metadrenalines are summarized in Table 1 (adapted from reference).[33]

Several studies have demonstrated that plasma and urinary O-methylated catecholamine metabolites, normetadrenaline (NMA) and metadrenaline (MA) have high diagnostic sensitivity and specificity, which is essential for the biochemical diagnosis of PPGL (Table 2).[34–53]

While there have been differences observed in the diagnostic sensitivity and specificity of UMets and PMets using different analytical methodologies, to date, there has not been a multicentre comparison using the gold standard method[1] of liquid chromatography tandem mass spectrometry (LC-MS/MS) for analysis.

Measurement of 3-methoxytyramine (3-MT) is not recommended for the investigation of PPGL, but it has the potential to distinguish patients with and without metastases and may be useful in identifying patients with inherited forms of PPGL.[54–56]

3-MT is a diagnostically more sensitive biomarker of tumoural DP production than plasma or urinary DP in patients with mutations in the succinate dehydrogenase type B (*SDHB*) gene.[54–56]

The greatest challenge associated with the interpretation of UMets and PMets results is the 'borderline-positive reference range' in patient populations with a low prevalence of PPGL.

In such cases, a false-positive result (increase of PMets and or UMets in the absence of a tumour) due to a confounding factor such as concomitant drug therapy or a physiological increase in catecholamine release is more likely than true-positive result (increase in UMets and or PMets due to the presence of a tumour) (Table 3). Borderline increases in PMets or UMets have been defined as anything between one and three times the upper limit of the reference interval.[5]

Defining the pretest probability of a PPGL in an individual patient is essential to the appropriate interpretation of results, which should not solely be based on the magnitude of the increase above the reference range.[5]

Assurance when one evaluates the importance of a borderline result can be gained by collecting a repeat plasma or urine sample under standardized low-stress conditions, for example, collecting a fasting plasma sample in the supine position after 20 min rest and avoiding urine collections after exercise.[1] Darr et al.[49] recently reported that the collection of a plasma sample in a non-fasting ambulant population can give false-positive rates of up to 30% compared with a 5% false-positive rate in patients, where the samples were collected under supine and fasted conditions.

In contrast, Boote et al.[52] reported in a small study that diagnostic sensitivity and specificity were acceptable for PMets when a sample was collected in a seated position for detection of PPGL. However, it is the authors' view that where practicable samples should be collected after fasting in the supine position.

Table 1. Potential advantages and disadvantages of measuring plasma and urine metadrenalines.

Factor	Plasma		Urine	
	Advantages	Disadvantages	Advantages	Disadvantages
Clinical utility	Reflect free metadrenalines produced directly by tumour			Measured after deconjugation, thus in large does not reflect fraction directly produced by tumour
Sample collection	Single sample is required, therefore more convenient for patient	Increased cost if patient is brought to clinic	Relatively little cost to health service as sample collected as an outpatient	Inconvenient for patients to collect 24 h sample. Often not collected reliably
Measurement		More difficult to measure than UMets as they are present at picomolar concentrations and the matrix is more complex than urine	Analytically less challenging to measure than PMets as they are present at micromolar concentrations and the matrix is less complex than plasma	
		Sample must be collected on ice, centrifuged and frozen within hours of collection	UMets more stable and can be processed with no urgency in an unpreserved container	
Patient preparation	Easier to control the influence of diet and medication on sympathoadrenal excitation	Sample should be collected in supine position and fasted state	Patients do not have to fast	Harder to control the influence of diet and medication on sympathoadrenal excitation
Utility in CKD	Test can be used in chronic kidney disease			Test not useful in CKD

Note: Adapted from Pacak et al.[33]
CKD: chronic kidney disease; UMets: total fractionated urine metadrenalines; PMets: plasma-free metadrenalines.

Table 2. Diagnostic performance characteristics of plasma and urine metadrenalines.

Analytical method	Sampling position (refers to plasma assay only)	Plasma		Urine(24-h collection)		Reference
		Diagnostic sensitivity	Diagnostic specificity	Diagnostic sensitivity	Diagnostic specificity	
LC-ECD	Supine	99	89	97	69	[34]
LC-ECD	Seated	97	85			[35]
RIA	Seated	96	79	93	80	[36]
LC-ECD	Not stated	95	95			[37]
LC-ECD	Supine	100	97			[38]
EIA	Supine	97	86			[39]
LC-ECD	Not stated	100	98	86	95	[40]
EIA	Not stated	80	100			[41]
LC-ECD	Supine	96	89	95	86	[42]
LC-MS/MS	Seated	100	96			[43]
EIA	Seated	95	95			[43]
EIA	Seated	100	88			[44]
LC-MS/MS	Seated	100	95			[44]
EIA	Seated	94	94			[45]
EIA	Seated	91	99			[46]
EIA	Seated	89	90	93	78	[47]
EIA	Supine	96	97	89	95	[48]
LC-MS/MS	Seated	76	98	95	80	[49]
LC-MS/MS	Supine	94	97			[49]
EIA	Supine	96	95			[50]
LC-MS/MS	Supine	98	100			[50]
LC-MS/MS	Seated	96	76	96	94	[51]
LC-MS/MS	Seated	93	90			[52]
LC-MS/MS	Supine	100	75			[53]

Note: Data from studies published between 2002 and 2017. The performance characteristics vary according to cut-off used for metadrenalines.

LC-ECD: liquid chromatography-electrochemical detection; RIA: radioimmunoassay; EIA: enzyme immunoassay; LC-MS/MS: liquid chromatography tandem mass spectrometry.

Additional reassurance can be achieved by demonstrating similar patterns of NMA and MA in the plasma and urine, thus it is the authors' recommendation in such situations that paired samples are collected. Moreover, patients should have any medication that may cause an analytical interference or result in a pharmacological increase in MAs (Table 3) modified and/or any underlying conditions managed optimally before re-testing.[57–72]

Genetic evaluation

It is estimated that 30–40% of PPGL[73,74] have a genetic predisposition which can be found in one of at least 14 genes and resonate from a variety of functional classes (Table 4).[73–94]

Mutations discovered to date cluster into two groups. Cluster one mutations encompass genes that are involved with the activation of the hypoxic response via specific transcription factors known as hypoxia-inducible factors (HIFs). Mutations in the genes responsible for regulation of these transcription factors can result in HIF pathways becoming constitutively active, leading to pseudohypoxic conditions that result in cell proliferation and angiogenesis.[73,74]

Cluster 2 mutations affect genes that are involved with kinase signalling pathways (notably MAPK and mTOR pathways). This leads to the activation of downstream targets that promote cell proliferation and survival.[75–78]

Genetic testing is relatively expensive; therefore, only the most likely mutations are tested for in a given patient. The decision on which mutations to test for is guided by clinical presentation, biochemical testing and imaging. The clinical presentation of type-1 neurofibromatosis (NF-1) is usually apparent so that genetic

Table 3. Analytical and pharmacological factors responsible for potential interferences in the measurement and interpretation of metadrenalines.

Agent causing increase in plasma or urine metadrenalines	Cause of increase	Plasma			Urine			References
		NMA	MA	3-MT	NMA	MA	3-MT	
Phenoxybenzamine	Pharmacological	Y			Y			57
Amitriptyline, venlafaxine	Pharmacological	Y			Y			57,58
Moclobemide, phenelzine	Pharmacological		Y		Y	Y		57
Amphetamines, ephedrine, cocaine	Pharmacological	Y	Y		Y	Y		57
L-DOPA	Pharmacological			Y			Y	59
Banana, pineapple, shelled walnuts	Pharmacological			Y	Y		Y	60
Coffee, nicotine	Pharmacological	Y			Y			34
Curry leaves (methoxyhydroxybenzylamine)	Analytical[a]				Y	Y		61
Buspirone	Analytical[a]					Y		62
Paracetamol	Analytical[a]	Y	Y		Y	Y		63,64
Sulphasalazine	Analytical[a]	Y			Y			65
Mesalamine	Analytical[a]				Y			66
Methenamine	Analytical[a]				Y	Y		67
Amoxicillin	Analytical[a]				Y			68
L-DOPA	Analytical[a]	Y	Y	Y	Y	Y	Y	69
L-DOPA	Analytical[b]			Y			Y	70
Isoproterenol	Analytical[b]	Y						71
MDMA	Analytical[b]	Y						71
HMMA	Analytical[b]				Y			72
Isoetharine	Analytical[b]		Y					71
MDA	Analytical[b]		Y					71

NMA: normetadrenaline; MA: metadrenaline; 3-MT: 3-methoxytyramine; MDMA: 3,4-methylenedioxymethamphetamine; MDA: 3,4-methylenedioxyamphetamine; HMMA: 4-hydroxy-3-methoxymethamphetamine.
[a]Liquid chromatography-electrochemical detection method.
[b]Liquid chromatography tandem mass spectrometry method.

testing in not usually required.[79] Conversely, mutations in the *SDHx* gene can have major implications on prognosis so that knowledge of the specific mutation is important. The subunit *SDHB* is known to have a high likelihood of malignancy unlike mutations in *SDHA*, *SDHC*, *SDHD* and *SDHAF2* subunits.[76,77,83,85,86] However, with the increasing use and availability of next generation sequencing, the approach to genetic evaluation of patients with PPGL is likely to change from a less targeted approach looking for known mutations to one that will screen entire genes identifying both novel and known mutations.

The identification and understanding of the role of specific genetic mutations that predispose patients to PPGL increase the potential for the development of 'personalized medicine'. An example of this is the mutations that have been identified in the rearranged during transfection (*RET*) gene. This gene is responsible for the multiple endocrine neoplasia 2 (MEN-2) phenotype and its mutations are grouped into one of four levels (A–D), with patients carrying level D mutations having the greatest likelihood of developing medullary thyroid carcinoma (MTC).[73]

Syndromes associated with PPGL

MEN-2

MEN-2 is an autosomal dominant syndrome with *RET* proto-oncogene mutations associated with MTC, PPGL and hyperparathyroidism.[95] PPGL has a variable penetrance, depending on the familial kindred. Fifty per cent of patients with a mutation in *RET* will develop a PPGL at some point in their lives.[96] In only 25% of cases will it be the presenting disease, explaining why patients need to be screened lifelong for PPGL and certainly before any surgery. MTC carries almost 100% penetrance in these syndromes and can occur in patients under the age of five years depending on the codon affected.[97]

Table 4. Genes known to play a role in the development of PPGL (both hereditary and somatic) including associated syndromes and clinical and biochemical presentations.

Gene	Inheritance	Risk of malignancy	Syndrome	Features	References
VHL[a]	Hereditary	Low	Von Hippel–Lindau	RCC, retinal haemangioblastomas, pancreatic tumours, endolymphatic tumours, epididymal cysts	76,77
SDHA[a]	Hereditary	Unknown	–	GIST	76,77,83,85,86
SDHB[a]	Hereditary	High	Paraganglioma type 4	GIST and RCC	76,77,83,85–86
SDHC[a]	Hereditary	Low	Paraganglioma type 3	GIST and RCC	76,77,83,85,86
SDHD[a]	Hereditary	Low	Paraganglioma type 1	GIST, pituitary adenomas and RCC	76,77,83,85,86
SDHAF2[a]	Hereditary	Unknown	Paraganglioma type 2	Head and neck paraganglioma	75,76,84
HIF2A (EPAS1)[a]	Somatic	Unknown	Polycythaemia paraganglioma syndrome	Polycythaemia and somatostatinomas	80–82
FH[a]	Hereditary	Unknown	Reed syndrome	RCC, smooth muscle tumours in the skin and uterus	87
RET[b]	Hereditary and somatic	Low	Multiple endocrine neoplasia type 2	MTC, hyperparathyroidism, cutaneous lichen amyloidosis and marfanoid habitus	76,77
Neurofibromin[b]	Hereditary and somatic	Moderate	Neurofibromatosis type 1	'Cafe au lait' spots, multiple fibromas, optic pathway and brainstem gliomas, astrocytomas, soft tissue sarcomas	77,79
MAX[b]	Hereditary and somatic	Low	–	Mainly PPGL	78,89
TMEM127[b]	Hereditary	Low	–	RCC, PCC	88,90,91
KIF1B	Hereditary	Unknown	–	Neuroblastoma, medulloblastoma, ganglioneuroma, leiomyosarcoma and lung adenocarcinoma	93–95
HRAS	Somatic	Unknown	–	None reported	92

FH: fumarate hydratase; GISTs: gastrointestinal stromal tumours; HIF2: hypoxia-inducible factor 2; MAX: MYC-associated factor X; MTC: medullary thyroid carcinoma; RCC: renal cell carcinoma; MTC: medullary thyroid cancer; SDH: succinate dehydrogenase; TMEM127: transmembrane protein 127; VHL: von Hippel–lindau; RET: rearranged during transfection.
[a]Cluster 1 mutation.
[b]Cluster 2 mutation.

Succinyl dehydrogenase syndrome

The *SDHx* family of nuclear genes (*SDHA, SDHB, SDHC, SDHD*) encodes for the subunits of the mitochondrial enzyme SDH. A fifth nuclear gene (*SDHAF2* or *SDH5*) encodes a protein required for flavination of *SDHA*. Mutations in these genes are inherited in an autosomal-dominant manner and cause the development of single or multiple PPGL in the head and neck, mediastinum, abdomen and pelvis. The site of PPGL (dictated by the gene abnormality) indicates the likelihood of secretion and malignancy risk (34–97% in *SDHB*).[1,98]

Patients should be genetically screened for *SDHx* abnormalities in the case of head and neck paragangliomas, multiple PPGL (synchronous or metachronous), recurrent disease and early onset of PPGL (<45 years).[1,99]

Von Hipple–Lindau

Von Hipple–Lindau (VHL) is inherited in an autosomal-dominant manner in 80% of cases and is characterized by multiple vascular tumours in the eyes, brain and nervous system with benign and malignant

tumours in sympathetic ganglia, kidneys, pancreas and adrenal glands. The *VHL* gene is a tumour suppressor gene. VHL is divided into subtypes depending on the risk of PPGL and renal cell carcinoma.[100,101] Type 2 (A, B and C), characterized by missense mutations, is all high risk for PPGL. Prevalence of PPGL in this syndrome is 10–25%.[102] Mean age at diagnosis of PPGL in VHL is 30 years old.[103] Suggested VHL surveillance advises screening for PPGL from five years old.[101] Up to 20% of all PPGL are secondary to VHL, reinforcing the argument for genetic screening in young patients.

Neurofibromatosis type 1 (NF-1)

NF-1 is an uncommon autosomal-dominant disease that has a low risk (<1–2.9%) of PPGL.[104] However, PPGL can occur in the very young and there may be a higher risk of malignancy (7–12%).[104,105] Genetic screening for PPGL in neurofibromatosis is not routinely performed, but the diagnosis should be considered in NF-1 patients with hypertension.

Takotsubo syndrome

Takotsubo syndrome is an acute cardiac entity characterized by a left ventricular wall motion abnormality with a circumferential extension beyond that expected from the coronary artery supply and resulting in left ventricular ballooning during systole. PPGL can be the causative stress.[106] In 80 reported cases, men constituted a higher proportion (30%) of PPGL-induced Takotsubo syndrome as compared with all cases (4.5%). Also patients with PPGL were significantly younger (19.8 years).[107] Patients present frequently with cardiac symptoms, including chest pain, palpitations and dyspnoea, but abdominal pain can be a warning symptom in these patients.

Imaging

Imaging is an important part of diagnosis and treatment planning for patients with PPGL. Imaging may be anatomical (important for surgical planning) or functional to assess sites of possible metastases and to evaluate possible treatment options in surgically unresectable or extensive disease.

Anatomical imaging

CT

Abdominal CT is often how PPGL are incidentally diagnosed. PPGL are thought to account for about 1.5–14% of adrenal incidentalomas.[13–15] CT is a good method of the assessment of adrenal incidentalomas as benign adrenal cortical neoplasms will usually be fat filled and therefore have Hounsfield units (HUs) of <10 (with no contrast). Unfortunately, many CTs are performed with intravenous contrast, which makes the HU an unreliable assessment. CT can also be used to assess the absolute and relative washout of an adrenal lesion. An absolute percentage washout of greater than 60% or a relative percentage washout of over 40% indicates a benign lesion. PPGL do not typically have a benign appearance on CT with HU >10, and often appear suspicious and may be reported as malignant due to their heterogenous appearances due to their hypervascularity and central necrosis. However, combined with abnormal MAs, these indeterminate or suspicious features can be diagnosed as a PPGL. A CT may suggest malignancy based on gross invasion into other glands and vascular structures or the presence of abdominal metastases.

MRI

MRI may be used to further define the characteristics of an indeterminate adrenal lesion on CT. Typically, a PPGL will light up with a hyperintense 'bright white' signal in T2-weighted images. MRI is also used for follow-up for *SDHx* families to prevent the excess radiation exposure associated with whole body CT.

Functional imaging

Metaiodobenzylguanidine scintigraphy

Metaiodobenzylguanidine (MIBG) is an analogue of NAd and accumulates in the neurosecretory granules. It is combined with [123]iodine to visualize on single-photon emission computed tomography (SPECT) imaging or fused with SPECT-CT for improved anatomical information. Specificities for phaeochromocytoma range from 70 to 100% and 84 to 100% for paragangliomas, with sensitivities of 85–88% and 56–76%, respectively.[108] To aid differentiation of pathological from physiological uptake, a tumour/liver ratio may be used, as difficulties can arise with increased physiological uptake and in small tumours. There is a question whether all PPGL patients need an MIBG, but the authors' unit still uses MIBG to assess for metastases and confirm localization. MIBG is more sensitive if performed while not on α-blockade.

Positron emission tomography computerized tomography

PPGL express somatostatin receptors and can be detected by somatostatin analogues when using

positron emission tomography computerized tomography (PET-CT). While traditionally octreotide scintigraphy has been the second-line functional imaging after MIBG, more recently, dotanoc/dototate has been used. Dotanoc has an increased sensitivity to a greater number of somatostatin receptors than octreotide.[109] [68]Gallium dotanoc PET-CT has a sensitivity of 80–96%, specificity of 85% and 100% accuracy for malignant PPGL and corresponding metastases.[109–111] These recent studies appear to show improved sensitivity compared with [18F]-fluorodeoxyglucose (FDG) PET. This also opens the possibility of dotatate therapy in metastatic disease.

FDG PET-CT

[18F]-FDG PET-CT relies on increased glucose metabolism in malignancy. While proven in many cancers, the role in PPGL is not clear. Studies have not clearly demonstrated a role for significantly differentiating between benign and malignant PPGL; there does, however, appear to be some evidence showing increased standardized uptake value max scores for PPGL in the *SDHx* syndromes[112] and in MIBG-negative PPGL patients. However, more recent data would suggest that [68]gallium dotanoc PET-CT has a higher sensitivity and increased sensitivity for individual metastatic lesions than [18F]-FDG PET-CT.[111]

Treatment

Treatment of PPGL relies on the expertise of endocrinologists, surgeons and anaesthetists. When performed within specialist teams and high volume units, these can be well controlled and safe operations. Surgery on unprepared patients with incidental PPGL can cause a crisis, resulting in significant hypertension, arrhythmias, stroke or death. The treatment of PPGL can be divided into medical, surgical and adjuvant treatment in malignancy. The treatment of a PPGL crisis is medical and supportive treatment of organ failure.

Medical treatment

Alpha-adrenergic receptor blockade is the mainstay of medical treatment for PPGL. Typically, phenoxybenzamine has been the agent of choice as a non-competitive and non-selective alpha-receptor antagonist. However, doxazosin can be used as a competitive, short-acting selective α_1 receptor blocker.[113] There is some evidence that doxazosin may cause less postoperative hypotension.[114] Li et al.[114] demonstrated less intra- and postoperative variability in blood pressure with doxazosin compared with phenoxybenzamine.

During α-blockade, it is important that fluid balance is monitored to ensure that the vasodilation produced is being supported by adequate fluid intake. This is usually adequate orally, but is often supplemented by an intravenous infusion of crystalloid fluid the night before surgery. Once the α-blockade is complete with a satisfactory postural blood pressure drop of 20–40 mmHg, a reflex tachycardia may develop, and at this point, it is safe to introduce a β-blocker to reduce the risk of tachycardias and arrhythmias. However, the patient should be α-blocked before the introduction of a β-blocker. Alpha-blockers can also be given intravenously, for example phentolamine can be used in a PPGL crisis or immediately perioperatively. Calcium channel blockers can also be used, although less commonly.

Surgical treatment

Abdominal PPGL can be removed by an open adrenalectomy if large or malignant, laparoscopic adrenalectomy or retroperitoneoscopic (through the back) adrenalectomy for smaller lesions (usually <4 cm). A predominantly no touch technique is important, as pressure on the lesion causes a spike in secretion of catecholamine. Any PPGL surgery carries additional increased risks of stroke, myocardial infarction and death as compared with normal adrenal surgery due to the extremes of hypo- and hypertension that can occur in surgery despite α- and β-blockades. It is therefore essential that these operations are performed in specialist centres. If the lesion is suspicious of a malignant PPGL, then it is important to achieve clear margins in the surgical resection, and this may mean resection of surrounding structures if invaded by the tumour.

Postsurgical therapy

Routinely, no adjuvant therapy is required for a benign PPGL. The difficulty is predicting and defining malignancy in these tumours. Paragangliomas have a higher risk of being malignant than phaeochromocytoma. Surveillance imaging, the recurrence of symptoms or biochemically positive results, may reveal metastases or local recurrence and therefore confirm malignancy. Malignant tumours are rare and therefore adjuvant treatment is not well characterized. Adjuvant treatment is usually only employed when metastases are present and often requires a multimodal approach. The five-year survival rate for patients with metastatic disease is around 50%.[5] Review of a cohort of 90 patients in France with malignant PPGL assessed the natural history of PPGL and showed a progression-free survival of 46% at one year indicating that active surveillance of disease progression is a valid option,[115] especially when

treatment options are limited. Malignant PPGL that are MIBG negative have a particularly poor prognosis; treatment options for these patients are poorly defined.

MIBG therapy

PPGL tumours and metastases that are positive on imaging for ^{123}I-MIBG can be treated with MIBG therapy in the form of ^{131}I-MIBG, which emits beta radiation. A number of studies have been published on this topic, but are not comparable due to study design making it difficult to draw reliable conclusions on the impact of ^{131}I-MIBG therapy. Yoshinaga et al.[116] prospectively recruited patients with metastatic neuroendocrine tumours for MIBG therapy. Forty-eight patients had malignant PPGL. Forty-five (94%) had previous treatment including surgery (79%), chemotherapy (50%) or standard radiotherapy (23%). Fifty-seven per cent of the patients received repeated MIBG therapy. Of the PPGL patients, 86% showed partial remission or stable disease by RECIST tumour size criteria: one partial regression, 54 stable disease and 10 progressive disease. In this study, no significant changes were seen in blood pressure at the first follow-up, but at the last follow-up, a significant reduction in systolic blood pressure was seen. Rutherford et al.[117] performed a retrospective review of 22 patients with PPGL assessed by World Health Organization (WHO) response criteria for symptomatic response, hormonal response and tumour size response. The patients were treated with surgery (86%), chemotherapy (32%) and radiotherapy (4%).

Nineteen per cent of patients showed complete or partial radiological response with 59% showing stable disease at six months. This study also demonstrated an improvement in hormone secretion and symptoms, but these factors had no significant effect on survival. A 68% five-year overall survival was seen in this study with a median survival of 17 years. A phase 2 prospective study showed 22% complete response or partial remission and 35% showed progressive disease at one year. Overall five-year survival was 64% with higher doses of MIBG.[118] Toxicity and side-effects of MIBG therapy can be significant and dose dependent. Side-effects are seen in 47–54% and include nausea, hypertension, abdominal pain, neutropaenia, hypothyroidism, ovarian failure and bone marrow suppression.[116–118] Dotanoc therapy with [90]yttrium-dotanoc and [177]lutetium-dotanoc can also be used for therapy based on uptake and success in neuroendocrine tumours.

Chemotherapy

Chemotherapy regimens that have been used for palliative chemotherapy include CVD (cyclophosphamide, vincristine and decarbazine) which gave a median progression-free survival of 5.4 months (2–26 months)[119] and on systematic review also reduced catecholamine secretion in 56% in combination therapy.[120] Temozolomide has been used as a single agent chemotherapy and associated with a tumour response and progression-free survival of 13.3 months in patients with SDHB mutations.[121] Chemotherapy is often used with other therapies and therefore it can be difficult to attribute which therapy is producing the effect. Many patients actually die from catecholamine excess, and hence the reduction in catecholamines is a significant benefit but combination with α-blockers and β-blockers will be required with a heavy tumour load and secretion.

Molecular-targeted therapy

Sunitinib is a tyrosine kinase inhibitor that is an effective antiangiogenic agent that targets vascular endothelial growth factor receptors 1 and 2 that are overexpressed in some metastatic PPGL.[122]

Progression-free survival is similar to that achieved using chemotherapy at 4.1 months.[123] The PI3K/Akt/mTOR pathway is thought to be involved in the pathogenesis of metastatic PPGL. mTOR inhibitors have been shown to have antitumour effects on PPGL cells in animal models.[124] Trials are underway to further investigate the clinical applications.

Histological evaluation

Macroscopic features

Phaeochromocytoma are soft, encapsulated tumours with a yellow/brown to red cut surface (Figure 1(a)) and may weigh from just a few grams to up to 4 kg. Larger tumours can show areas of necrosis, cystic degeneration or haemorrhage. They usually have a thin rim of compressed adrenal cortex peripherally. If potassium dichromate is added to fresh tumour, it will turn dark brown (chromaffin reaction).

Microscopic features

Microscopically, the tumour cells have round to oval nuclei with a prominent nucleolus and may contain cytoplasmic inclusions. The cells have a finely granular basophilic or amphophilic cytoplasm and are usually arranged in nests (Zellballen pattern) surrounded by a rich vascular network (Figure 1(b)). Marked nuclear pleomorphism and hyperchromasia can be seen (Figure 1(c)), but similar to capsular and vascular invasion, this in itself is not a reliable indicator of malignancy. Mitoses are rarely found. Occasionally, the tumour cells may have an oncocytic appearance due
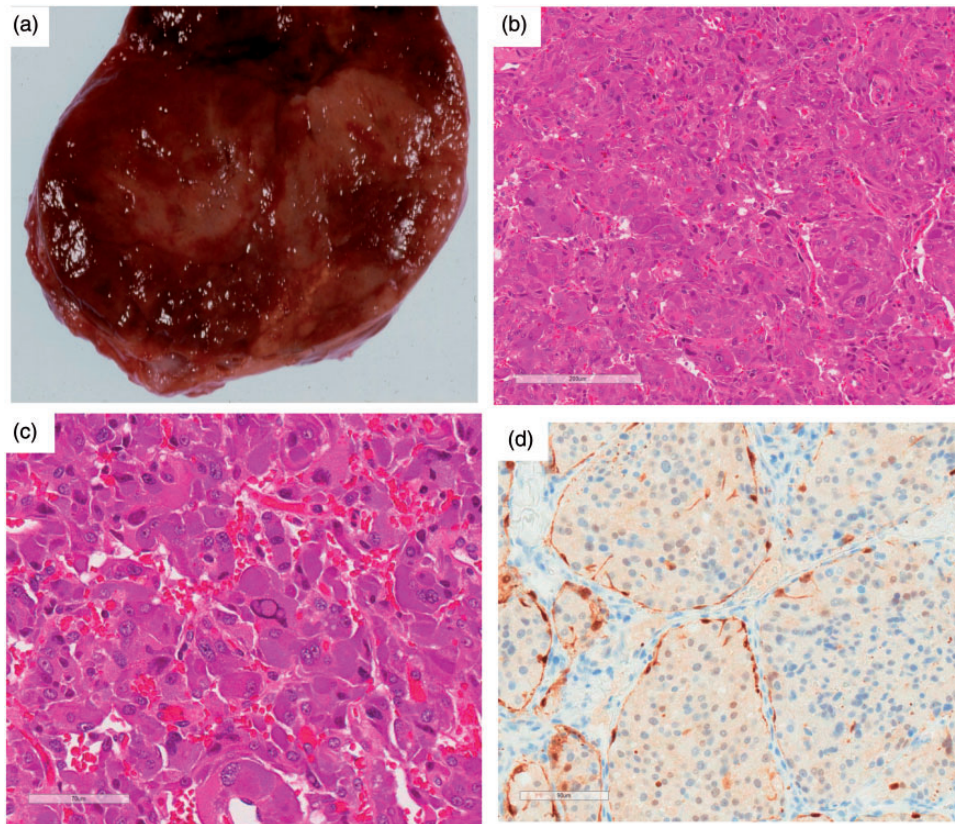
Figure 1. Pathological features observed in phaeochromocytoma. (a) Enlarged adrenal gland; (b) nested pattern (haematoxylin and eosin staining); (c) nuclear pleomorphism (haematoxylin and eosin staining staining); (d) sustentacular cells demonstrated by immunocytochemistry for S-100 protein.

to the presence of large numbers of mitochondria. Other features include ganglion-like cells, dystrophic calcification and melanin pigment,[125] and the presence of amyloid.[126] The nests are outlined by sustentacular cells, which provide structural support and are not visible with routine staining techniques, but can be highlighted with S-100 immunocytochemistry (Figure 1(d)).

PPGL can be associated with other tumours of the adrenal medulla, such as ganglioneuroma, ganglioneuroblastoma or neuroblastoma, and with other tumours such as adrenal cortical adenoma, spindle cell sarcoma[127] or neuroendocrine carcinoma.[128] Hyperplasia of the adjacent adrenal medulla can be an indication of MEN-2 syndromes, but it is difficult to identify and genetic screening is more accurate.[129]

Immunohistochemical profile

PPGL express the neuroendocrine markers chromogranin, synaptophysin and neurone-specific enolase. They may express HMB45 (due to a close histogenic link with melanocytes[130]) and more rarely cytokeratins and vimentin. S-100 highlights the sustentacular cells.

Behaviour

The WHO states that malignancy is defined only by the presence of metastasis to sites where paraganglial tissue is not normally found.[2] While specific, this is not sensitive and is not helpful in predicting tumour behaviour or the need for close patient follow-up in cases where metastasis is not identified. There are no absolute histological criteria to predict malignancy, and multifactorial approaches have been suggested. The PASS (Phaeochromocytoma of the Adrenal gland Scoring Scale) system is summarized in Table 5.[131] All tumours that metastasized were reported to have scores $\geqslant 4$. Others have reported significant interobserver and intraobserver variations in the use of the PASS system[132] and a more recent paper proposed an alternative system called the GAPP score (Grading system for Adrenal Phaeochromocytoma and Paraganglioma) which is summarized in Table 6.[133] This subdivides the tumours into well-differentiated (0–2 points), moderately differentiated (3–6 points) and poorly differentiated (7–10 points). It requires further validation to assess its reproducibility and ability to predict malignant behaviour. Current UK national guidance suggests that these scoring systems are not sufficiently robust to be mandated as part of routine reports.[134]

Table 5. Phaeochromocytoma of the Adrenal gland Scoring Scale.

Histological feature	Score
Large nests of cells or diffuse growth >10% of tumour volume	2
Necrosis (confluent or central in large cell nests)	2
High cellularity	2
Cellular monotony	2
Presence of spindle-shaped tumour cells (even focal)	2
Mitotic figures (>3 per 10 high power fields)	2
Extension of tumour into adjacent fat	2
Vascular invasion	1
Capsular invasion	1
Profound nuclear pleomorphism	1
Nuclear hyperchromasia	1
Total possible score	20

Table 6. Grading system for Adrenal Phaeochromocytoma and Paraganglioma.

Parameters	Points scored
Histological pattern	
Zellballen	0
Large and irregular cell nest	1
Pseudorosette (even focal)	1
Cellularity	
Low (<150 cells/10 μm^2)	0
Moderate (150–250 cells/10 μm^2)	1
High (more than 250 cells/10 μm^2)	2
Comedo necrosis	
Absence	0
Presence	2
Vascular or capsular invasion	
Absence	0
Presence	1
Ki67 labelling index (per cent)	
<1	0
1–3	1
>3	2
Catecholamine type	
Adrenaline type	0
Noradrenaline type	1
Non-functioning type	0
Total maximum score	10

10 μm^2: number of tumour cells in a square of a 10 μm observed under high power magnification (400×).

Follow-up

Guidance on the long-term follow-up of patients operated on for PPGL has been published by the European Society of Endocrinology.[135] In brief, this guidance recommends patients should be followed-up annually for 10 years to screen for local or metastatic recurrence or new tumours, unless they are high risk (i.e. young patient or those with genetic disease). If this is the case, patients should be followed annually for life.

From a biochemical perspective, it is proposed that PMets or UMets are measured two to six weeks postoperation in patients with elevated MAs preoperatively, and then annually to screen for local or metastatic recurrence or new tumours. If PMets or UMets remain elevated postoperatively, imaging should also be performed within three months following surgery.

In addition, it is proposed that plasma chromogranin A is measured preoperatively in patients with normal PMets or UMets (including 3-MT) and postoperatively when chromogranin A is raised preoperatively.

In biochemically inactive PPGL, imaging should be considered every one to two years to screen for local or metastatic recurrence or new tumours.

Genetic testing should be considered in all patients with histologically proven PPGL because over one-third of patients with PPGL have mutations in the susceptibility genes, and the presence of mutations has implications for the patient and family members.

The extent of genetic testing is influenced by a number of factors including cost and the diagnostic algorithm employed for genetic testing.[83]

Conclusion

PPGL is a rare disease but with significant clinical consequences. Advances in the biochemical diagnosis, genetic assessment and screening have seen significant developments in recent years. While surgical treatment is curative in many cases, the treatment of malignant disease remains a challenge.

Ethical approval

Not applicable.

Guarantor

ASD and SLS.

Contributorship

All authors contributed to this review.

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