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## 31.1 Clinical Presentation

Pheochromocytomas and paragangliomas (PPGLs) are catecholamine-producing neuroendocrine tumors that respectively arise from chromaffin or paraganglial tissue at adrenal and extra-adrenal locations [1]. Paragangliomas usually form from chromaffin cells associated with paravertebral sympathetic ganglia, most usually in the abdomen (e.g., organ of Zuckerkandl), but also in the pelvic areas (e.g., bladder) and less frequently in the thorax (e.g., mediastinum). Paragangliomas may also form at the neck and skull base, but these derive from parasympathetic or carotid body-associated tissue and usually do not produce significant amounts of vasoactive catecholamines.

As a result of tumoral secretion of catecholamines, patients with high blood pressure and symptoms of catecholamine excess are those in whom PPGLs are most frequently suspected. The tumors are also frequently identified among patients who undergo imaging for unrelated purposes and in whom incidental abdominal or adrenal masses (i.e., incidentalomas) are found. Patients with germline mutations of an increasing number of PPGL susceptibility genes represent another group in whom the tumors are now often found in the setting of routine screening due to hereditary risk.

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PPGLs usually occur during middle age, but in 10–20% of cases present during childhood [2], the latter usually associated with a hereditary cause reflecting the younger age of presentation of hereditary than sporadic tumors. The clinical presentation of PPGLs can vary enormously from severe cardiovascular emergencies associated with sustained or paroxysmal hypertension and symptoms of catecholamine excess to a completely normotensive and asymptomatic presentation often found among patients screened due the presence of an incidentalomas or an underlying hereditary predisposition [3, 4].

### 31.1.1 Prevalence

Autopsy studies have indicated prevalences of PPGLs of 0.05–0.13%, mostly reflecting cases that remained undetected during life [5–7]. From reported annual incidences of PPGLs of between two and five cases detected per million per year [8, 9], translating to lifelong prevalences of 0.013–0.033%, it seems clear from the autopsy series that most PPGLs remain undetected throughout life, contributing to premature death. Nevertheless, prevalences at autopsy have dropped from 0.13% in the 50-year period before 1982 [5] to 0.05% in the 20-year period up until the turn of the century [6, 7], suggesting improved diagnosis during life. Presumably there have been further improvements in diagnosis over the subsequent 15 years, so that annual detection rates at some centers might be expected to reach ten or more per million.

Among patients with hypertension, the prevalence of PPGLs has been estimated at 0.6% [10], at least fourfold higher than overall prevalence rates. It can therefore be expected that prevalences are higher, possibly reaching 2% among patients with sustained or paroxysmal hypertension and symptoms of catecholamine excess. This is in agreement with findings that among unselected patients screened for PPGLs, prevalences of PPGLs range from 0.8 to 1.6% [11–13]. Among patients with adrenal incidentalomas, prevalences of pheochromocytoma are higher, between 4 and 9% [14, 15], with an overall prevalence of 7% indicated by review of 29 studies performed between 1982 and 2002 [16]. Depending on the mutation, prevalences can be even higher in patients with a hereditary predisposition to PPGLs, reaching 40% in patients with multiple neoplasia type 2 (MEN 2) [17].

### 31.1.2 Signs and Symptoms

Most patients with PPGLs have classical symptoms due to the effects of excessive circulating concentrations of catecholamines (Table 31.1). Reported frequencies of symptoms depend however on the studied populations and are often biased by the retrospective nature of studies. Some patients have been reported as normotensive and completely asymptomatic, particularly those in whom tumors are diagnosed based on screening because of hereditary predisposition or of findings of an incidentaloma [4]. In rare cases, tumors may synthesize no or little catecholamines or only produce dopamine [18, 19].

**Table 31.1** Frequency (%) of signs and symptoms

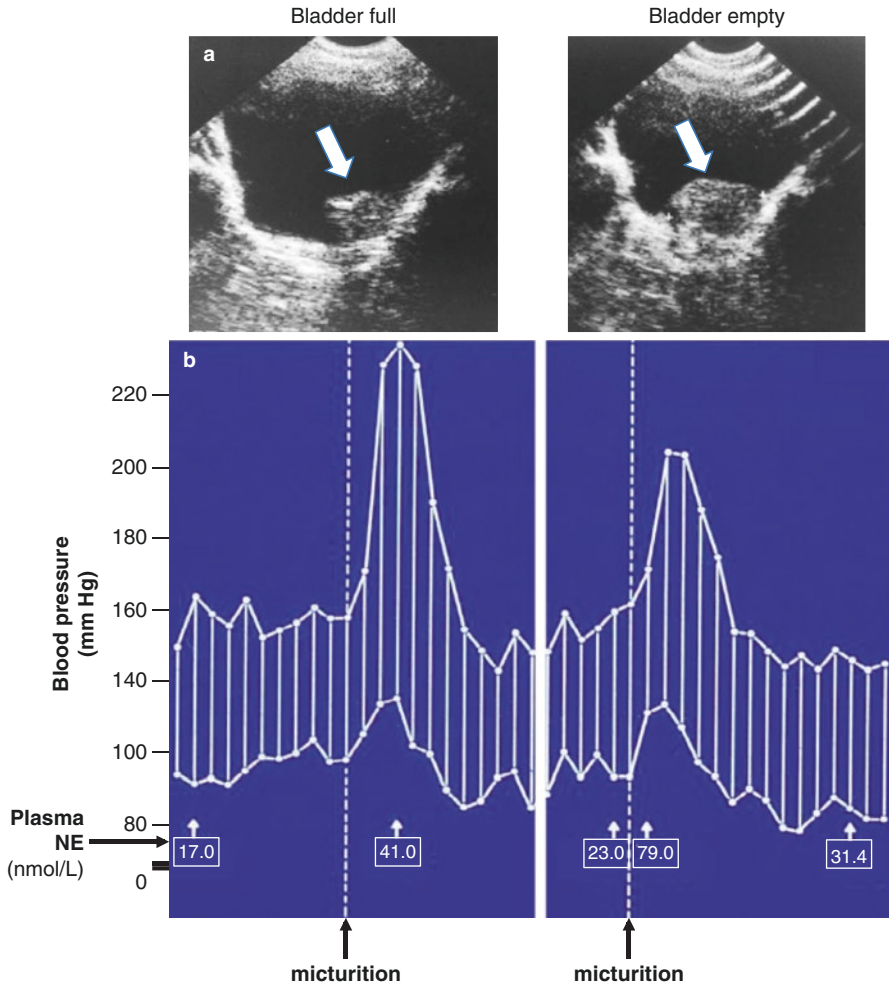
Headache	70–90
Palpitations	50–70
Diaphoresis	55–75
Hypertension	85–90
– Sustained	50–60
– Paroxysmal	50
Orthostatic hypotension	10–60
Pallor	40–60
Hyperglycemia/diabetes	40–60
Nausea/vomiting	20–45
Anxiety/panic attacks	20–40
Fatigue	20–40
Gastrointestinal: constipation, ileus	10–15
Weight loss	15–40%

Signs and symptoms of PPGLs usually present paroxysmally, consequent to the hemodynamic and metabolic actions of peak levels of catecholamines (Fig. 31.1). Such episodes usually last between a few to 60 min and can occur spontaneously or may be provoked by drugs (e.g., steroids, antiemetics), anesthesia, tyramine-containing foods, or mechanical factors. Adverse reactions to medications can be particularly problematic (Table 31.2). The frequency of such episodes varies from once daily to only a few times per month.

The hallmark that usually triggers clinicians to consider the diagnosis of PPGL is hypertension. At least 50% of patients have chronic but usually labile hypertension with short-lasting episodes of high surges in blood pressure. Specific blood pressure patterns often feature prominent daytime variability, an absent or blunted diurnal blood pressure rhythm, orthostatic hypotension, and more rarely hypotension [20, 21]. A small percent of patients present with shock, which has been suggested to occur particularly in epinephrine- or dopamine-secreting tumors [22].

Apart from hypertension, there is wide constellation of other established signs and symptoms, dominated by the classic triad of paroxysmal headache, palpitations, and diaphoresis (Table 31.1). In addition many other nonspecific symptoms may be encountered, including nausea, tremulousness, anxiety, panic attacks, weight loss, and gastrointestinal symptoms such as constipation and vomiting. Hyperglycemia and even overt diabetes mellitus in young lean hypertensive subjects should arouse suspicion of the tumor. Due to the nonspecific nature of most symptoms, there are many other clinical conditions, mostly associated with increased sympathetic activity, that mimic presence of a catecholamine-producing tumor [3].

In about 10% of patients with PPGLs, elevations in blood pressure may evolve into a hypertensive crisis with subsequent organ damage involving acute coronary syndrome, left ventricular heart failure, Takotsubo cardiomyopathy, arrhythmias, or stroke [21, 23–25]. Occasional patients may also present with multisystem crisis associated with an IL-6-mediated acute inflammatory syndrome, high-grade fever (>40 °C), and leukocytosis [21], evolving into renal failure, pulmonary edema, encephalopathy, and lactic acidosis. Delayed treatment is associated with a high fatality rate [23].



**Fig. 31.1** Paroxysmal hypertension in a patient with a paraganglioma of the urinary bladder. Sonograms of urinary bladder in the patient before and after micturition are shown in *panel A*. Blood pressure profiles recorded before, during, and after micturition on two separate days are shown in *panel B*. Blood samples were taken at intervals and plasma concentrations of norepinephrine (NE) measured as shown for the five time points of collections

Several factors account for the variable clinical picture of PPGLs, including tumor size, biochemical phenotype, co-secreted peptides, and underlying pathogenic mutations. In general, larger tumors are associated with larger elevations in catecholamines and more prominent signs and symptoms, but this association may be lost when the tumors contain substantial hemorrhage or necrosis. Patients with epinephrine-producing tumors are more likely to display paroxysmal symptoms such as palpitations, tremulousness, and anxiety than tumors producing merely norepinephrine [26–28]. This may in part reflect the more prominent

**Table 31.2** Classes of drugs potentially responsible for adverse reactions in patients with PPGLs

Drug class	Examples
$\beta$ -adrenergic receptor blockers	Propranolol, metoprolol, atenolol, labetalol
Hormones (steroids, peptides)	Prednisone, dexamethasone, methylprednisolone, glucagon
Dopamine D2 receptor antagonists	Metoclopramide, sulpiride, chlorpromazine, droperidol
Antidepressants (tricyclics, SSRIs, MAO inhibitors)	Amitriptyline, imipramine, clomipramine, paroxetine, fluoxetine, phenelzine, moclobemide
Sympathomimetics	Ephedrine, phenylpropanolamine, fenfluramine, phentermine (dex)amphetamine, methylphenidate, cocaine
Anesthetics (opioid analgesics, neuromuscular blocking agents)	Pethidine, morphine, tubocurarine, succinylcholine, atracurium besilate

SSRIs: selective serotonin uptake inhibitors

MAO: mono amine oxidase

beta<sub>2</sub>-adrenergic effects of epinephrine, but as detailed later may also reflect differences in secretory characteristics. Tumors that produce predominantly dopamine are rare, presenting mainly as paragangliomas, particularly in the head and neck. Patients with such tumors are usually normotensive and asymptomatic [18, 29]. Presence of nausea or orthostatic hypotension has been reported in several patients with dopamine-producing PPGLs [18, 30]. Given the widely varying clinical spectrum of signs and symptoms, a meticulously taken detailed medical history and physical examination are essential for timely diagnosis of this treacherous tumor.

### 31.1.3 Incidentalomas

As many as or more than 25% of all pheochromocytomas are now being diagnosed after presentation as an adrenal incidentaloma [31–33]. Many cases of abdominal or thoracic paragangliomas are also being discovered after imaging for nonspecific reasons such as abdominal pain or due to other mass effects of tumors [18, 33]. Due to the high prevalence of PPGLs among such patients, combined with the substantial proportion of normotensive and asymptomatic cases, routine screening for PPGLs is widely recommended for all patients with incidentally discovered masses, regardless of the presence or absence of signs and symptoms [16, 33–35].

As indicated in one study, biochemical phenotypic features and other tumor characteristics differ between patients presenting with normotensive incidentally discovered adrenal pheochromocytomas and those with similarly sized tumors associated with overt signs and symptoms [36]. Specifically tumors from patients who were normotensive showed lesser increases in both urinary metanephrines and catecholamines than in patients who were hypertensive. This suggested that differences in biochemical features might contribute to discovery of such tumors as incidentalomas rather than more classically secondary to hypertension and symptoms of catecholamine excess.

### 31.1.4 Hereditary Disease

At least a third of PPGLs are inherited due to germline mutations of more than 13 tumor susceptibility genes identified to date [37, 38]. The most well-established hereditary causes of PPGLs are those associated with syndromic presentations including neurofibromatosis type 1 (NF 1) due to mutations of the *NF1* gene, multiple endocrine neoplasia type 2 (MEN2) due to mutations of the rearranged during transfection (*RET*) gene, von Hippel-Lindau (VHL) syndrome due to mutations of the *VHL* gene, and familial paraganglioma syndromes caused by mutations of genes encoding succinate dehydrogenase subunits B and D (*SDHB* and *SDHD*). Other less frequent forms of hereditary PPGLs can result from mutations of succinate dehydrogenases A and C (*SDHA* and *SDHC*), succinate dehydrogenase complex assembly factor 2 (*SDHAF2*), transmembrane domain protein 127 (*TMEM127*), MYC-associated factor X (*MAX*), prolyl hydroxylase 2 (*PHD2*), fumarate hydratase (*FH*), and malate dehydrogenase 2 (*MDH2*).

Prevalence of PPGLs associated with the above mutations varies according to penetrance of disease and incidence of mutations. For NF1, although relatively common (1:3000), penetrance of pheochromocytoma is low with not more than 5% of patients developing the tumors [39]. In contrast, the penetrance of pheochromocytoma for *RET* mutation carriers reaches 40–50% [17], while for VHL syndrome it averages 20% with variability according to the particular mutation [40]. For some mutations of the *SDHD* gene penetrance has been reported to reach up to 100% [41]. Among patients with *SDHD*, *SDHAF2*, and *MAX* mutations, disease is transmitted to offspring paternally, skipping a generation with maternal transmission [42–44]. For most of the recently discovered tumor susceptibility genes, penetrance has not yet been precisely established, this requiring long-term follow-up of non-index cases.

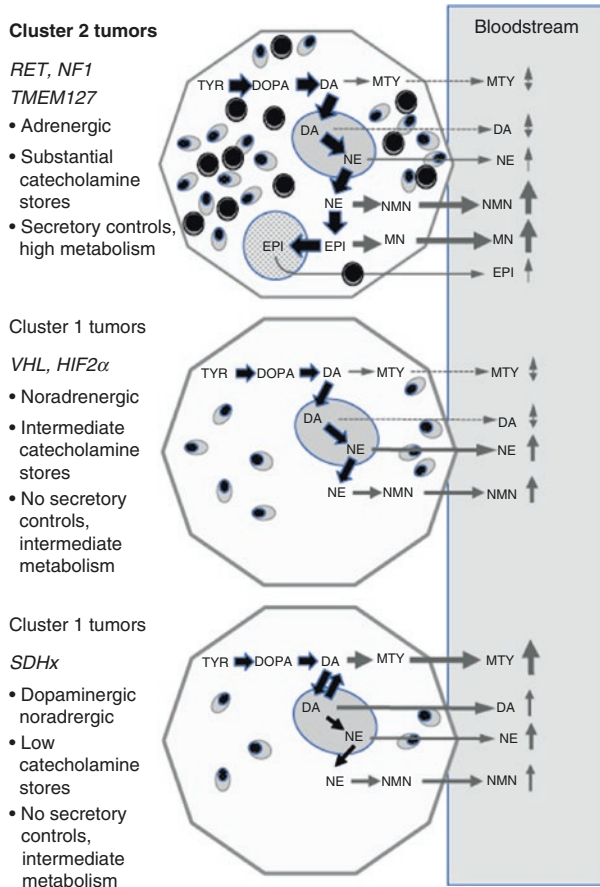
Despite the variability and uncertainty of disease risk, it is widely recognized that all patients carrying mutations of PPGL susceptibility genes should undergo periodic screening for the tumors. For patients with VHL syndrome and MEN2, such screening at specialist centers is already well established and clearly results in diagnosis of tumors at an earlier stage when tumors are small and patients are normotensive and asymptomatic [28, 45]. For all there is an emerging need for personalized management according to risk. Patients with *SDHB* mutations, who carry a high risk for metastatic PPGLs [46], provide an example of those who might particularly benefit from earlier detection of disease before metastatic involvement.

Due to the rich hereditary background of PPGLs, it is recommended by Endocrine Society clinical practice guidelines that all patients with PPGLs receive counseling about possible genetic risk and that genetic testing should be particularly encouraged for several groups of patients [47]: (1) those with a positive family history of PPGLs or tumor susceptibility gene mutations, (2) those with syndromic features, (3) those with PPGLs occurring at a young age, (4) those with multifocal or bilateral adrenal tumors, (5) those with paragangliomas in whom

there is high risk of mutations for genes encoding succinate dehydrogenase subunits, and (6) those with metastatic disease in whom there is a high risk of *SDHB* mutations. The underlying rationale for such testing is that identification of a gene mutation provides a context for routine screening programs that can result in earlier detection of PPGLs and other neoplasms, thereby reducing morbidity and mortality. For patients with aggressive disease in whom surgical intervention is not an option, new developments on the horizon also make it likely that establishing the underlying mutation can provide a rationale for therapies that target downstream signaling pathways [48].

For PPGLs, the pathways leading to tumorigenesis are being rapidly elucidated consequent to their rich hereditary background [37, 49, 50]. As originally indicated by gene expression profiling, the various types of hereditary PPGLs fall into one of two main cluster groups according to the mutation and downstream affected signaling pathways [37]. Mutations of *RET*, *NF1*, *TMEM127*, and *MAX*, associated with cluster group 2, all involve activation of RAS and kinase signaling pathways and lead to well-differentiated adrenal pheochromocytomas with low susceptibility to malignancy. In contrast, mutations of *VHL*, *SDHB*, *SDHD*, *SDHC*, *SDHA*, *SDHAF2*, *PHD2*, and *FH*, associated with the cluster group 1, all result in stabilization of hypoxia-inducible factors (HIFs) leading to activation of hypoxia-angiogenic pathways. Apart from increased expression of hypoxia pathway genes, these tumors are also characterized by increased expression of the *HIF2 $\alpha$*  itself and occur at an earlier age at both adrenal and extra-adrenal locations compared to the more differentiated cluster 2 tumors [51, 52]; this is suggested to reflect importance of transient expression of *HIF2 $\alpha$*  during early differentiation of sympathoadrenal progenitors, with stabilization at the protein level leading to inhibition of both apoptosis and differentiation [53].

Support for involvement of *HIF2 $\alpha$*  in development of cluster 1 PPGLs has come from identification of *HIF2 $\alpha$*  itself as a tumor susceptibility gene, in almost all cases involving somatic mutations [54]. Importantly, *HIF2 $\alpha$*  mutations show mosaicism, indicating occurrence during embryogenesis [55]. Nevertheless, even with the commonality of *HIF2 $\alpha$*  in development of cluster 1 PPGLs, there are additional differences in signaling pathways among cluster 1 PPGLs. For *HIF2 $\alpha$* , *VHL*, and *PHD2* mutations, stabilization of HIFs reflects the direct central tumorigenic mechanism. In contrast, for mutations of genes encoding succinate dehydrogenase subunits and other Krebs cycle enzymes (e.g., fumarate hydratase), stabilization of HIFs occurs secondary to wider actions of the elevated cellular levels of oncometabolites, succinate, or fumarate [48]. These oncometabolites inhibit not only the prolyl-hydroxylases that facilitate HIF degradation but also other alpha-ketoglutarate-dependent hydroxylases, such as histone and DNA demethylases. As a result, PPGLs resulting from mutations of genes encoding Krebs cycle enzymes exhibit a hypermethylator phenotype, turning off expression of numerous genes involved in restricting growth and controlling differentiation [56]. The result is that among cluster 1 PPGLs, those due to mutations of genes encoding Krebs cycle enzymes, and *SDHB* in particular, are the most aggressive and poorly differentiated (Fig. 31.2).



**Fig. 31.2** Catecholamine phenotypic features in PPGLs according to mutation. Cluster 2 tumors due to *RET*, *NF1*, and *TMEM1* mutations are well differentiated, metabolizing tyrosine (TYR) to L-dopa (DOPA) by tyrosine hydroxylase, then to dopamine (DA) by aromatic amino acid decarboxylase, then to norepinephrine (NE) by dopamine  $\beta$ -hydroxylase after uptake into noradrenergic vesicles, and then to epinephrine (EPI) by phenylethanolamine N-methyltransferase (PNMT) after leakage of NE into the cytoplasm. DA is metabolized to methoxytyramine (MTY), NE is metabolized to normetanephrine (NMN), and EPI is metabolized to metanephrine (MN), all conversions catalyzed in the cytoplasm by catechol-O-methyltransferase. Cluster 1 tumors due to *VHL*, *HIF2 $\alpha$* , and *SDHx* mutations do not express PNMT so that these tumors do not produce EPI or MN. Also, these tumors, although having lower catecholamine stores compared to cluster 2 tumors, have poorer secretory controls than cluster 2 tumors and secrete catecholamines at higher rates. Tumors due to *SDHx* mutation are particularly poorly differentiated and often produce large amounts of MTY



## 31.2 Biochemistry

### 31.2.1 Catecholamine Synthesis, Storage, Secretion, and Metabolism

Synthesis, storage, secretion, and metabolism of catecholamines in PPGLs vary substantially depending on expression of catecholamine biosynthetic and secretory machinery, this as outlined above determined by underlying gene mutations [57, 58] (Fig. 31.2). The well-differentiated cluster 2 type pheochromocytomas all express phenylethanolamine N-methyltransferase (PNMT), which converts norepinephrine to epinephrine. Norepinephrine and epinephrine are stored in electron microscopically distinct secretory vesicles, the presences of which differ in cluster 1 and 2 mutated tumors [28].

Catecholamine secretion primarily involves exocytosis in which storage vesicles fuse with the plasma membrane and extrude their catecholamine contents into the extracellular space. This secretory process is a highly regulated calcium-dependent process responsive to neuronal input or secretagogues for evoked but controlled release of catecholamines. While PPGLs lack the former control, they can be influenced by secretagogues, but vary considerably in expression of the cellular secretory machinery responsive to regulatory control. Cluster 1 mutated tumors not only lack expression of PNMT, but in contrast to well-differentiated cluster 2 tumors also exhibit poorer expression of other key catecholamine biosynthetic enzymes and components responsible for storage and regulated secretion of catecholamines [57] (Fig. 31.2).

As a consequence of the above differences, cluster 1 tumors lack production of epinephrine and also contain lower overall stores of catecholamines [58] (Fig. 31.2). Furthermore, due to their relative lack of regulated secretory pathway machinery, cluster 1 tumors also secrete the limited amounts of catecholamines they produce in a more continuous or constitutive fashion compared to cluster 2 tumors. Thus, in contrast to cluster 1 PPGLs, cluster 2 epinephrine-producing pheochromocytomas, such as those in patients with MEN 2 or NF1, are characterized by highly concentrated stores of catecholamines and relatively low rates of catecholamine secretion. These tumors can, however, be easily provoked to secrete catecholamines in response to secretagogues and other stimuli, which may provide the basis for why epinephrine-producing tumors have been described as more often producing paroxysmal hypertension compared to norepinephrine-producing tumors.

The above differences along with differences in co-secretion of bioactive peptides are likely responsible for some of the highly variable clinical manifestations of chromaffin cell tumors, but as yet there has been no fully prospective study to firmly establish such a link between underlying mutations to differences in presentation of disease. There are, however, forms of undifferentiated PPGLs for which a link seems clear. These in particular involve patients who have PPGLs due to mutations

of the *SDHB* gene which appears to be associated with further downregulated expression of catecholamine phenotypic features due to epigenetic silencing secondary to actions of elevated succinate to inhibit alpha-ketoglutarate-dependent enzymes involved in regulating DNA methylation [56]. As a consequence, tumors in patients with *SDHB* mutation contain the lowest amounts of catecholamines, among all PPGLs; catecholamine contents are also characterized by relative high proportions of dopamine [58, 59]. The tumors often reach large sizes before their discovery, which may reflect both relative paucity of signs and symptoms and diversion of energy from maintaining chromaffin-like phenotypic features to enhanced growth. Consequently, these tumors carry a high risk of malignancy.

Most other PPGLs contain large amounts of catecholamines, particularly norepinephrine, in about 50% of cases additional epinephrine and a variable amount of dopamine [58]. Tumor contents and secretion of dopamine are impacted by the efficiency of dopamine beta-hydroxylase in converting the dopamine to norepinephrine after the former amine is translocated into secretory vesicles [60]. Importantly, the catecholamines stored in secretory granules exist in a highly dynamic equilibrium with the surrounding cytoplasm, with passive outward leakage into the cytoplasm counterbalanced by inward active transport under the control of vesicular monoamine transporters [61]. For all catecholamines, whether stored in sympathetic neurons, adrenal chromaffin cells, or tumors derived from adrenal or extra-adrenal chromaffin cells, most initial metabolism takes place within the cells where the catecholamines are synthesized [62].

In sympathetic nerves, the presence of monoamine oxidase (MAO), but absence of catecholamine-O-methyltransferase (COMT), leads to deamination of norepinephrine to dihydroxyphenylglycol (DHPG). This primary norepinephrine metabolite is derived largely from norepinephrine leaking from storage vesicles, but is also derived from reuptake of the transmitter back into nerves [62]. Only a small amount of norepinephrine escapes reuptake; some of this is metabolized extraneuronally to normetanephrine or DHPG, while a remaining small proportion (<5%) reaches the circulation as norepinephrine. In adrenal chromaffin cells and tumors of chromaffin cells, the additional presence of COMT leads to production of metanephrine from epinephrine, normetanephrine from norepinephrine, and methoxytyramine from dopamine [63]. This production again depends on leakage of catecholamines from storage vesicles, a continuous process that is independent of exocytotic release of catecholamines, which makes a relatively minor contribution to production of metanephrine. Thus, over 90% of all circulating metanephrine is normally derived from metabolism of epinephrine within adrenal chromaffin cells [64]. These cells also make the single largest contribution to circulating normetanephrine (at least 24%), with the rest from norepinephrine metabolized to normetanephrine in non-neuronal and non-chromaffin extraneuronal cells. Continuous production of the O-methylated metabolites within chromaffin cells and their tumor derivatives explains why measurements of plasma-free and urine deconjugated metanephrines provide advantages over measurements of catecholamines, which can be released by some tumors intermittently or in low amounts. Other catecholamine metabolites are produced in various organs and tissues of the body and also are not as useful as the metanephrines for diagnosis of PPGLs.

Vanillylmandelic acid, for example, is almost exclusively formed in the liver as the end product of catecholamine metabolism and derived mainly from DHPG produced in sympathetic nerves [65].

### 31.2.2 Biochemical Diagnosis

The superior diagnostic accuracy of measurements of plasma-free metanephrines over other tests has been clearly outlined by several independent studies [66–71], with several others confirming the high diagnostic accuracy of either plasma or urinary fractionated metanephrines for identifying patients with PPGLs [72–74]. With this evidence at hand, it has been a simple matter for Endocrine Society clinical practice guidelines on PPGLs to stipulate that initial testing for PPGLs should always include measurements of plasma-free or urinary fractionated metanephrines [47]. All other available tests, including urinary or plasma catecholamines, urinary vanillylmandelic acid, urinary total metanephrines (measured by spectrophotometric methods), and chromogranin A, are unnecessary and generally inappropriate for initial screening of PPGLs, but may be employed for follow-up confirmation of positive results of plasma-free or urinary fractionated metanephrines or in specific presentations of disease.

If used correctly with appropriate analytical methods and reference intervals, measurements of plasma-free metanephrines in particular provide diagnostic sensitivity approaching 100% with diagnostic specificity of at least 95% [74]. Over 90% of PPGLs show elevations of normetanephrine, about 50% elevations of metanephrine, and 45% elevations of methoxytyramine, with about 70% showing some combination of increases of normetanephrine with metanephrine or methoxytyramine or both. Moreover, increases are usually well in excess of twofold above the upper cutoffs. Such magnitudes of increases and combinations of increases are rare in patients without PPGLs, providing high positive predictive value in over 80% of patients with PPGLs. For these patients it is simply a matter of locating the tumor. For the other minority of patients with PPGLs in whom false positives are difficult to distinguish from true positives, biochemical diagnosis can be made using the clonidine test when elevations involve normetanephrine or by follow-up to establish increasing concentrations over time.

With measurements of plasma metanephrines by mass spectrometry and employing appropriate preanalytical precautions and reference intervals, diagnosis of PPGLs is simple [75]. Common problems, however, occur with the use of inaccurate analytical methods (e.g., immunoassays), incorrect reference intervals, and inappropriate preparation of patients for blood sampling. For the latter, patients should be sampled after 30 min supine rest and should not be under physiological or mental stress that might increase sympathoadrenal activity. Sampling in the seated position or under any form of stress carries a high likelihood of false positive results. When measurements involve plasma methoxytyramine, sampling should be carried out after an overnight fast.

At many centers, however, clinicians have problems following the above recommendations, and there can also be problems with availability or adequacy of

laboratory measurements or reference intervals for plasma-free metanephrines [75]. For this reason, measurements of urinary fractionated metanephrines provide an alternative to plasma-free metanephrines.

### 31.2.3 Interpretation of Positive Biochemical Test Results

In addition to indicating the presence of PPGLs, usually with high positive predictive value, patterns of increases in plasma free metanephrines can also be used to predict tumor size, location, underlying mutations, and metastatic involvement [75]. As outlined earlier, mutations of different genes are associated with differences in expression of catecholamine biosynthetic enzymes and thus differences in patterns of increases of normetanephrine, metanephrine, and methoxytyramine [76]. Patients with cluster 2 types mutations, such as those involving *RET* and *NFI* genes, almost all show increases in plasma metanephrine, with or without increases in normetanephrine. In contrast, PPGLs due to cluster 1 type mutations, such as those involving *VHL*, *SDHD*, and *SDHB* genes, do not express PNMT and do not produce epinephrine. Consequently, cluster 1 type tumors are associated with increases of normetanephrine, but not metanephrine. Furthermore, in patients with *SDHB* and *SDHD* mutations, there are often increases in methoxytyramine, which reflect the more immature nature of these tumors compared to other PPGLs.

Phenotypic immaturity, as indicated by increases in plasma methoxytyramine, is also associated with higher likelihood of metastatic involvement. In this context increases in plasma methoxytyramine provide the only currently available biomarker for metastatic involvement [59]. Although substantial increases of methoxytyramine are present in only about 60–70% of all cases of metastatic PPGLs, when present they are important to consider as an indicator of malignancy.

Since the extent of increase in plasma metanephrines is dependent on size of vesicular stores of catecholamines, the magnitude of increases in the metabolites can be used to roughly indicate mean tumor diameter [77]. Additionally, increased plasma metanephrine almost always indicates an adrenal pheochromocytoma or recurrence of an adrenal pheochromocytoma, whereas large increases in methoxytyramine relative to normetanephrine are indicative of extra-adrenal tumors. Such biochemical information indicating tumor size and location can be useful for subsequent imaging or interpretation of imaging results.

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## 31.3 Tumor Localization

### 31.3.1 Anatomical Imaging

In general, imaging studies to locate a PPGL should be ordered once there is clear biochemical evidence for the presence of the tumor [47]. Exceptions to this rule are emergency situations where an immediate diagnosis and treatment are required [78]. Imaging studies without an established biochemical diagnosis are not cost-effective

and entail a risk for diagnostic confusion with incidentaloma, thus complicating the work-up further. The first choice imaging modality for PPGL is computed tomography scanning (CT) before and after contrast administration of the abdominal and pelvic areas [47]. More than 95% of all PPGLs are located in these areas.

CT is in general preferred over magnetic resonance imaging (MRI) because of its superior spatial resolution. The sensitivity of CT for detecting pheochromocytomas is over 90%, but lower for paragangliomas and for recurrent or metastatic tumors [79, 80]. Since CT has no high reliability for elucidating the nature of a mass, the specificity for correct identification of the mass is moderate, even with consideration of imaging features such as density, contrast enhancement, and washout [81].

Although MRI imaging with or without gadolinium enhancement has a superior sensitivity over CT for detecting paragangliomas [79], again as with CT, specificity of MRI falls short due to features that may impair signal intensity such tumor necrosis or hemorrhage [81]. Apart from extra-adrenal paragangliomas, MRI is also indicated in specific patient groups, such as those with metastases, with intracardiac or head and neck PGLs, with postoperative surgical clips, and with iodine allergy. Patients in whom radiation exposure should be kept to a minimum are also candidates for MRI, including children, pregnant women, and others with known germline mutations who are likely to undergo repeated imaging studies [47].

### 31.3.2 Functional Imaging

Since anatomical imaging is insufficient for assessing multifocality or metastatic disease and is not specific for establishing the diagnosis, a complementary functional imaging step is often required after anatomical imaging [82, 83]. The aim of functional imaging is thus to establish the nature of a mass and identify other focal or metastatic lesions. For this purpose several radiolabeled ligands targeting specific cell membrane and/or vesicular catecholamine transport systems are available. Some ligands are employed for single photon emission computed tomography (SPECT), such as  $^{123}\text{I}$ -MIBG, while others are used for positron emission tomography (PET), such as  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) or  $^{68}\text{Ga}$ -DOTATATE.

The most widely available functional imaging ligand is  $^{123}\text{I}$ -MIBG. Sensitivity with  $^{123}\text{I}$ -MIBG SPECT for detection of pheochromocytoma approaches 100%, but is considerably less for extra-adrenal paragangliomas (56–75%) and metastases, particularly when associated with underlying SDHx mutations (<50%) [84–86]. A specific advantage of using  $^{123}\text{I}$ -MIBG is the potential to identify patients with metastatic PPGLs who may benefit from treatment with therapeutic doses of  $^{131}\text{I}$ -MIBG [83].

PET imaging agents used for functional imaging of PGLs include  $^{18}\text{F}$ -fluorodopamine ( $^{18}\text{F}$ -FDA),  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG),  $^{111}\text{In}$ -DTPA-pentetreotide,  $^{68}\text{Ga}$ -DOTATATE, and  $^{68}\text{Ga}$ -DOTATOC [83, 86]. The diagnostic accuracies of these different compounds vary, depending on specific clinical features, such as tumor location, genetic mutation, and metastatic involvement, requiring personalized considerations for best choice of agent as available. Since many PPGLs overexpress subtype 2 somatostatin receptors, radiolabeled somatostatin

receptor ligands can be particularly useful for localization. Such ligands developed for PET imaging, including  $^{68}\text{Ga}$ -DOTATATE and  $^{68}\text{Ga}$ -DOTATOC, have shown particularly excellent diagnostic accuracy for head and neck paragangliomas and SDHB-related metastatic disease [87–89].

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## 31.4 Management

### 31.4.1 Preoperative Management

Surgical outcomes of patients with PPGLs have improved considerably over the last 50 years with a current perisurgical mortality rate of less than 1%. This can be attributed to improved presurgical medical preparation of patients as well as emergence of multidisciplinary teams and sophisticated approaches to anesthesiological management. Although most patients are in the long term cured by tumor removal, postsurgical recurrence rates average 16.5% [90].

Elective surgical removal of a catecholamine-producing tumor should be preceded by preoperative medical preparation to prevent or minimize hazardous complications due to massive release of catecholamines from the tumor, particularly provoked by mechanical manipulation during surgery [47, 91]. Such precautions are indicated in all patients in whom elevations of plasma or urinary metanephrines indicate a catecholamine-producing tumor, regardless of the presence or absence of symptoms or whether patients are hypertensive or normotensive. Although some retrospective small series of patients have questioned the need for medical preparation, there are no randomized trials documenting that refraining from medical pretreatment is safe. Since it is impossible to predict the course during surgery in individual patients, a patient-tailored strategy of preoperative blockade provides the safest approach.

The mainstay for successful medical pretreatment remains  $\alpha$ -adrenoceptor antagonist therapy using the noncompetitive inhibitor, phenoxybenzamine, or the competitive inhibitor, doxazosin [91, 92]. Evidence from randomized trials showing benefits of one over the other are lacking [47]. Calcium channel blockers are generally not used as first-line blocking agent but do hold a place as an add-on drug to  $\alpha$ -adrenoceptor blockade. Similarly, the catecholamine-synthesis inhibitor  $\alpha$ -methylparatyrosine (metyrosine) can be employed as an add-on treatment to  $\alpha$ -adrenoceptor blockade when required [91, 93]. A  $\beta$ -adrenoceptor antagonist, such as atenolol or metoprolol, can also be included several days before surgery to prevent tachyarrhythmias, but only after  $\alpha$ -adrenoceptor blockade [91].

The recommended duration of pharmacological pretreatment in elective patients is 7–14 days, but this is based mainly on expert opinion. The target blood pressure level is less than 130/80 mm Hg in the sitting position with a systolic blood pressure in the upright position higher than 90 mm Hg [47, 91]. A presurgical high-sodium diet and high fluid intake during preparation are helpful to circumvent postsurgical hypotension [91]. Close postsurgical surveillance for at least 24 h is essential for detection and proper treatment of hypotension and hypoglycemia. In specific patients undergoing bilateral or major unique adrenal surgery, the possibility of adrenal insufficiency is the first and most important consideration in situations of postsurgical hypotension.

### 31.4.2 Surgical Management

Surgical removal of pheochromocytomas by minimal invasive laparoscopic tumor resection is first choice treatment with the posterior retroperitoneal approach preferred in patients with pheochromocytoma [94]. Paragangliomas may also be resected by laparoscopic surgery depending on tumor size, relation to other organs, and on the experience of the surgeon [95]. Retrospective cohort studies have shown that patients operated by laparoscopy experience less blood loss and have a shorter stay in hospital as compared to conventional open surgery [96, 97]. In patients with underlying mutations such as those with MEN2 and VHL, adrenal-sparing surgery is indicated when technically feasible. Leaving some remnant adrenocortical tissue in situ avoids or postpones need for lifelong steroid replacement therapy for adrenal insufficiency, but this benefit should be balanced against the increased risk of tumor recurrence [98–100].

### 31.4.3 Follow-Up

Following surgical removal of PPGLs, all patients should undergo follow-up to ascertain whether the tumor has been removed completely [101]. For patients with presurgically elevated plasma or urine metanephrines, measurements can be repeated at 2–6 weeks after surgery. Persistently elevated test results suggest residual disease that should then be confirmed by additional imaging studies.

Since there is a persistent risk of recurrent disease after apparently complete resection of an initially discovered PPGL, it is important that follow-up is continued in the long term well after surgical resection [102]. Risk of recurrence is higher in young patients (<20 years), in those with syndromic presentations, paragangliomas, and patients with large tumors. However, there is no “safe” tumor size below which the risk is zero. Thus, follow-up is recommended in all operated patients annually for at least 10 years, but continuing thereon in high-risk patients, such as those who are young, carry an underlying germline mutation or who present with an extra-adrenal or large tumor. Follow-up should include an annually taken medical history, physical examination including blood pressure, and measurements of plasma or urinary fractionated metanephrines.

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