MANAGEMENT OF ENDOCRINE DISEASE

Clinical management of paragangliomas

Eleonora P Corssmit and Johannes A Romijn¹

Department of Endocrinology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands and ¹Department and Division of Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Correspondence
should be addressed
to E P Corssmit

Email

E.P.M.van_der_Kleij-
Corssmit@lumc.nl

Abstract

Paragangliomas (PGLs) are rare vascular, neuroendocrine tumors of paraganglia, which are associated with either sympathetic tissue in adrenal (pheochromocytomas (PCCs)) and extraadrenal (sympathetic paraganglioma (sPGLs)) locations or parasympathetic tissue of the head and neck paragangliomas (HNPGs). As HNPGs are usually benign and most tumors grow slowly, a wait-and-scan policy is often advised. However, their location in the close proximity to cranial nerves and vasculature may result in considerable morbidity due to compression or infiltration of the adjacent structures, necessitating balanced decisions between a wait-and-see policy and active treatment. The main treatment options for HNPG are surgery and radiotherapy. In contrast to HNPGs, the majority of sPGL/PCCs produces catecholamines, in advanced cases resulting in typical symptoms and signs such as palpitations, headache, diaphoresis, and hypertension. The state-of-the-art diagnosis and localization of sPGL/PCCs are based on measurement of plasma and/or 24-h urinary excretion of (fractionated) metanephrines and methoxytyramine (MT). sPGL/PCCs can subsequently be localized by anatomical (computed tomography and/or magnetic resonance imaging) and functional imaging studies (¹²³I-metaiodobenzylguanidine-scintigraphy, ¹¹¹In-pentetreotide scintigraphy, or positron emission tomography with radiolabeled dopamine or dihydroxyphenylalanine). Although most PGL/PCCs are benign, factors such as genetic background, tumor size, tumor location, and high MT levels are associated with higher rates of metastatic disease. Surgery is the only curative treatment. Treatment options for patients with metastatic disease are limited. PGL/PCCs have a strong genetic background, with at least one-third of all cases linked with germline mutations in 11 susceptibility genes. As genetic testing becomes more widely available, the diagnosis of PGL/PCCs will be made earlier due to routine screening of at-risk patients. Early detection of a familial PGL allows early detection of potentially malignant PGLs and early surgical treatment, reducing the complication rates of this operation.

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Invited Authors' profile

Johannes (Hans) A Romijn is Professor of Medicine and Chairman of the Division of Medicine, Academic Medical Center, University of Amsterdam, The Netherlands. Prof. Romijn trained in internal medicine in the Academic Medical Center, University of Amsterdam. In 1997 he was appointed as Professor in Clinical Nutrition and in 1998 as Professor of Endocrinology and Chairman of the Department of Endocrinology, Leiden University Medical Center (LUMC). He served as president of the Dutch Endocrine Society from 2002–2006. In 2010 he was appointed chairman of the Division and the Department of Medicine of the Amsterdam Medical Centre (AMC). His research focuses on pathophysiology and treatment of pituitary diseases and of diabetes.

Eleonora Corssmit graduated in Medicine from the University of Amsterdam and the Academic Medical Centre, Amsterdam, The Netherlands. She is currently an Assistant Professor at the Department of Medicine, Section of Endocrinology, at the Leiden University Medical Centre in Leiden, the Netherlands. Her clinical and scientific work is focussed on adrenal tumors, especially pheochromocytoma and paraganglioma.

Introduction

Paragangliomas (PGLs) are rare vascular, neuroendocrine tumors of paraganglia cell clusters originating from the neural crest that have co-migrated with the autonomic nervous system (1). PGLs are associated with either the sympathetic tissue in adrenal (pheochromocytomas (PCCs)) and extra-adrenal locations (sympathetic PGLs (sPGLs)) or the parasympathetic tissue of the head and neck paragangliomas (HNPG, formerly called glomus tumors) (1). PGLs can be found from the skull base to the sacrum. From all PGLs, PCCs have the highest relative incidence. In 340 unselected PGL patients, about 73% of the patients had PCC, 9% had sPGL, and 20% had HNPG (2, 3). HNPGs have a predilection for the middle ear (tympanic PGL), the dome of the internal jugular vein (jugular PGL), the bifurcation of the common carotid arteries (carotid body PGL), or along the vagal nerve (vagal PGL), sPGL for the mediastinum (from the thoracic sympathetic chain) and the abdominal and pelvic para-aortic regions, including the organ of Zuckerkandl.

The prevalence of PGL is unknown but has been estimated to lie between 1:6500 and 1:2500 in the USA (4). Their prevalence is higher in autopsy series (1:2000), suggesting that many tumors remain undetected (5). The annual incidence has been reported to be two to ten cases per million (6). In hypertensive patients, sPGL/PCCs are found in 0.1–0.6%, in adrenal incidentalomas in about 5% (7). PGLs may occur in all ages, with the highest incidence between 40 and 50 years and with an approximately equal sex distribution (3, 8). At least one-third of PGL/PCCs is hereditary, and this percentage is likely to increase with the discovery of new susceptibility genes (9). Most PGL/PCCs are benign, ~10–15% are malignant, defined by the presence of metastatic spread in sites where chromaffin tissue is normally absent, such as lymph nodes, liver, bone, and lungs (10, 11).

Clinical picture

Sympathetic PGL/PCC

The majority of sPGL/PCCs produces catecholamines, in advanced cases causing symptoms of catecholamine excess. In unselected series, 10–15% of cases are asymptomatic. The clinical presentation is variable due to different profiles of catecholamines secreted, presentation of symptoms related to tumor mass or other organ involvement in syndromic forms, and desensitization of adrenoreceptors (most likely due to

long-term exposure to high circulating catecholamine levels) (12). Therefore, sPGL/PCC is also called ‘the great masquerader’. Hypertension, continuous or paroxysmal, is the most common feature of advanced PCCs and sPGLs. Typical symptoms are paroxysms of severe headache, palpitations, and diaphoresis, ‘the classic triad’. Paroxysms can last minutes to hours, vary in interval and occur spontaneously or be triggered by direct stimulation of the tumor (e.g. micturition in case of bladder localization), physical activity, diagnostic procedures, or certain drugs (e.g. metoclopramide, glucagon, and glucocorticoids) (13, 14). Other symptoms may include anxiety, nausea, vomiting, and weakness (15). In addition, hyperglycemia, resulting from metabolic actions of catecholamines, may be the presenting symptom (16). As symptoms and signs are usually atypical, a long delay in diagnosis is not uncommon. Because this can lead to severe and potentially fatal cardiovascular complications (e.g. sudden death, myocardial infarction, heart failure, and cerebrovascular accidents), a prompt diagnosis is warranted.

Head and neck paraganglioma

HNPGs, which belong to the domain of the ear nose throat doctor, usually grow slowly. Nonetheless, patients with HNPGs need to be checked by endocrinologists, because some of these tumors produce catecholamines and some of these patients have an increased risk to develop sPGL/PCCs. The majority of HNPGs has a tumor doubling time of more than 10 years (17). Because of this slow growth rate, HNPGs may remain clinically silent for years. Although these tumors are usually benign and only a minority (20–30%) produces catecholamines, predominantly methoxytyramine (MT) (18, 19), their location in the close proximity of nerves and vascular structures often results in considerable morbidity due to compression or infiltration of the adjacent structures, causing symptoms such as hearing loss, tinnitus, dysphagia, and cranial nerve palsy. Carotid body tumors are the most common HNPG, usually presenting as a painless cervical mass (20). Large compressive tumors may result in cranial nerve paralysis. Vagal body tumors present as painless neck masses, located behind the angle of the mandible, occasionally accompanied by dysphagia and hoarseness (21). Tympanic and jugular foramen tumors most commonly present as a vascular middle ear mass causing pulsatile tinnitus and

hearing loss. Difficulties in speech, swallowing, and airway function may be the result of dysfunction of cranial nerves traversing the jugular foramen (22).

Making a diagnosis by biochemical evaluation and imaging

Sympathetic PGL/PCC

Clinical suspicion of sPGL/PCCs or the presence of an adrenal incidentaloma should be followed by biochemical testing to rule out the potentially lethal diagnosis of a sPGL/PCC. The biochemical diagnosis of sPGL/PCCs consists of the demonstration of hypersecretion of catecholamines (epinephrine, norepinephrine, and dopamine (DA)) or their *O*-methylated metabolites metanephrine (MN), normetanephrine (NMN), and MT (23). Since MNs have a longer half-life and are produced continuously within tumor cells, being the catecholamines converted to MNs by the high methyltransferase activity of chromaffin tissue, while catecholamines are intermittently secreted, measurement of plasma free MNs and/or 24-h urinary excretion of fractionated MNs provides the best test with an excellent sensitivity of >96% for detecting sPGL/PCCs (24). Since dietary constituents (especially caffeine, nicotine, and amine-rich foods) or medication (especially antihypertensive and tricyclic antidepressant medication) can interfere with the analysis of or increase plasma levels and urinary excretion of catecholamines or its metabolites, ideally collection is performed while abstaining from these substances and/or stopping antihypertensive drugs or changing medication to the α blocker doxazosin (25, 26). In addition, plasma should be sampled after fasting and in the supine position for 30 min, to minimize sympathoadrenal activation (13, 27, 28). Restriction of amine-rich foods is mainly necessary for the measurement of MT (29). With regard to stopping or changing medication, which is often difficult, a reasonable alternative is not to do this and repeat testing in case of elevated results. In case of only mildly elevated values, false-positive results are usually reflected by larger increments in catecholamines as compared with MNs due to sympathoadrenal activation (30). In case plasma NMN is mildly increased, a clonidine suppression test may be useful to rule out sympathetic activation as the underlying cause, since values will normalize in case of sympathetic activation, but decrease <40% 3 h after administration of clonidine in case of a PGL (sensitivity 100% and specificity 96%) (31).

PGLs exhibit different biochemical properties as PCCs mainly produce epinephrine and norepinephrine, sPGLs norepinephrine and malignant PLGs norepinephrine, DA or no catecholamines due to a dedifferentiation of the enzymatic machinery (31, 32). Plasma levels of chromogranin A (CgA), secreted from neurosecretory vesicles along with catecholamines (33), are often elevated in both functioning and silent PGLs and particularly in malignant ones (34). CgA levels correlate with tumor mass, making it a useful tumor marker (35). Sensitivity for identifying PGLs is 83–89%. False-positive results, however, occur often due to liver or kidney failure or use of proton pump inhibitors (36).

After establishing a biochemical diagnosis, sPGL/PCC can be localized and staged by anatomical and functional imaging studies. Anatomical imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) have an excellent sensitivity (77–98 and 90–100% respectively) but lack specificity (29–92 and 50–100% respectively) for detecting PCC/sPGLs (37, 38). On CT, PCCs usually present as homogenous tumors with soft tissue density of more than 10 Hounsfield Units and uniform enhancement with contrast. However, larger PCCs may undergo hemorrhage and necrosis resulting in areas of low density (39). On MRI, PCCs present as a mass absent of fat on chemical shift, with a high signal on T2 sequences as a result of their hypervascularity (40). Tumors detected by anatomical imaging can subsequently be identified as PGL by functional imaging agents that specifically target the catecholamine synthesis, storage, and secretion pathway of chromaffin cells. ^{123}I - or ^{131}I -metaiodobenzylguanidine (MIBG) scintigraphy is the most widely available and used nuclear technique in the first-line functional imaging of PGL. MIBG has chemical similarities to NE and is taken up by the human NE transporter, which is expressed in most chromaffin cells and is normally responsible for catecholamine uptake (41). The sensitivity (83–100% for ^{123}I -MIBG and 77–90% for ^{131}I -MIBG respectively) and specificity (95–100% for both ^{123}I - and ^{131}I -MIBG) are high for primary tumors, being higher for PCCs than for PGLs (42, 43, 44); however sensitivity of MIBG-scintigraphy for metastasis is relatively poor (56–83%) (37, 45, 46, 47). In patients with negative MIBG-scintigraphy, other tracers may be used. Radiolabeled DA or dihydroxyphenylalanine (DOPA) may be used as tracers in positron emission tomography (PET) imaging. ^{18}F -DOPA PET has been confirmed to be useful in the evaluation of sPGL and HNPGL (48) (Fig. 1). For patients suspect for metastatic PGL, ^{18}F -fluoro-2-deoxyglucose (FDG) PET is recommended (sensitivity 74–100%) (26, 48, 49, 50), with the highest performance for metastatic succinate

Figure 1

¹⁸F-DOPA PET scan of a patient with a right-sided vagal body tumor (VBT) and a small left-sided carotid body tumor (CBT): (A) ¹⁸F-DOPA PET total body scan showing physiological uptake in the brain, heart, bile ducts and urinary tract, and pathological uptake in the HNPGs. (B) Fusion scan of ¹⁸F-DOPA PET scan with low-dose CT-scan, showing right-sided VBT. (C) Fusion scan of ¹⁸F-DOPA PET scan with low-dose CT-scan, showing left-sided CBT.

dehydrogenase B (SDHB)-related PCC/PGL (50). In addition, ¹¹¹In-pentetreotide scintigraphy may be useful in detecting MIBG-negative metastases (37). ¹²³I-MIBG scintigraphy is widely available, with a performance similar to PET scanning using ¹⁸F-fluorodopamine, ¹⁸F-DOPA, and ¹⁸F-FDG for PCC (26, 47), for PGL, or metastatic PCC/PGL. ¹²³I-MIBG scanning is inferior to ¹⁸F-FDG PET, ¹⁸F-DOPA PET or somatostatin receptor imaging with ¹¹¹In-pentetreotide scintigraphy (26, 49, 50).

Head and neck paraganglioma

MRI with pre- and post-contrast enhanced 3D time of flight MR angiography sequence represents the most important imaging technique for evaluation and characterization of HNPGs (51). MRI of HNPG provides more diagnostic information than does CT scanning, because of the better soft tissue contrasts as compared with CT (52). MRI enables multiplanar imaging of tumor extension and vessel encasement. Ultrasound has a limited diagnostic yield, but can be of use in imaging HNPG (53). ¹²³I-MIBG scintigraphy has a low sensitivity for the detection of HNPGs. ¹¹¹In-pentetreotide scintigraphy was shown to have a better sensitivity, lower than that of MRI. ¹⁸F-DOPA PET was shown to have a very good

sensitivity for the detection of HNPG (Fig. 1) (48), and can be advised as the first-line imaging method for HNPGs; if unavailable, ¹⁸F-FDG or somatostatin receptor scintigraphy can be used complementary to anatomic imaging studies (50).

Management

Sympathetic PGL/PCC

The treatment of choice for PCCs and sPGLs is surgical resection, preferably laparoscopically (54), but in case of a large tumor (in general >6 cm) with a higher risk of malignancy, conventional laparotomy should be considered. In order to minimize surgical complications (hypertensive crisis and arrhythmias), adequate pretreatment is necessary, consisting of α -blockade (doxazosin and phenoxybenzamin) titrated at orthostatic hypotension, if needed followed by addition of β -blockade (propranolol and atenolol), especially in case of tachycardia. The day before surgery, volume expansion of intravascular volume should be started by infusion of isotonic saline as these patients are in a constant status of volume depletion (55). Pretreatment reduces perioperative mortality to below 1% (56). Intraoperatively, hypertensive episodes are related with catecholamine release, mostly by direct manipulation of the tumor. In patients with bilateral PCC, laparoscopic cortical sparing adrenalectomy may be considered to avoid chronic glucocorticoid deficiency (57). Preoperative injection of ¹²³I-MIBG in combination with intraoperative use of a gamma probe may localize small lesions that are difficult to find (58, 59).

Postoperatively, severe hypotension can occur in case of hypovolemia, which is no longer opposed by catecholamine-induced intense vasoconstriction, and prolonged effects of the preoperatively started medication (α -blockers). In addition, hypoglycemia can occur due to the sudden decrease in catecholamines and thereby increase in insulin secretion. Two to four weeks postoperatively, plasma and/or urinary MN levels should be checked, and normalization indicates successful resection of the tumor. Usually blood pressure normalizes after the operation, depending on completeness of the resection, duration of pre-existing hypertension, and potentially coexisting other causes of hypertension. Since histology cannot differentiate between benign and malignant PGL/PCC and there is the possibility of recurrence of PCC, lifelong follow-up is advised for local recurrence and metastases (26). Postoperative follow-up with annual measurement of blood pressure and plasma and/or urinary MN levels is

advised in all patients previously treated for sPGL/PCC, with additional anatomical imaging if indicated (Fig. 2).

Head and neck paraganglioma

Treatment for HNPGL must be considered in relation to tumor growth velocity, biological activity of the tumor, patient age and medical condition, tumor size and site, and potential for treatment-related morbidity (17). As most tumors grow slowly, a wait-and-scan strategy is often advised (17). However, although HNPGLs are indolent tumors, tumor growth may lead to serious morbidity and cranial nerve impairment due to their location in close proximity to important neurovascular structures. The main treatment modalities for HNPGL are surgery and radiotherapy. A multidisciplinary team approach is recommended for the choice of treatment of most HNPGL except for the very small and easy-to-resect tumors. With surgery, it is possible to remove the tumor without recurrence. The rate of surgical complications rises with the size of the tumor (60). The most common complications are cranial nerve damage and vascular

complications (61, 62, 63, 64, 65, 66). Although Power *et al.* (67) showed that preoperative embolization simplified the conduct of the operation and reduced blood loss, it did not impact on cranial nerve damage. Coexisting sPGL/PCC should be resected before resection of a HNPGL. External beam radiotherapy and radiosurgery are alternative treatment modalities for HNPGL patients, resulting in local tumor control in 79–100%, and sometimes regression by producing fibrosis and vascular sclerosis (68). These may be first-line therapeutic strategies in patients with large growing tumors, in which resection may result in considerable morbidity, or after incomplete resection of tumor with intracranial or skull base invasion (68). The optimal choice of treatment is not clear at the moment, due to the absence of trials, selection bias, and differently defined criteria for surgery vs radiotherapy. Although some groups also propagate routine use of radiotherapy (64, 65), we advocate a wait-and-scan strategy, with intervention in case of tumor progression or concern about malignancy. Preoperatively and pre-radiotherapy, patients with HNPGL should be tested for MN excretion, and pharmacological preparation should

Figure 2

Stepwise approach for endocrine diagnosis, treatment, and follow-up in (hereditary) HNPGL/sPGL/PCC.

be started in positive cases (26, 66), with the exclusion of patients with solitary elevation of MT. In case of increased DA secretion, there is no certainty for a benefit of pre-operative pharmacological treatment. After successful resection of a solitary, nonhereditary biochemically silent HNPGL, patient can be discharged from further follow-up. In other cases, follow-up is advised, consisting of evaluation of catecholamine excess in biochemically active HNPGLs and ENT examination and MRI of the head and neck.

Malignant PGL

There is no definite histological rule that can be used for the diagnosis of malignant PGL (69, 70). Therefore, malignancy is defined by the presence of metastases: tumor spread to sites where chromaffin tissue is normally absent (10, 11). Nearly 10% of PCCs and 10–20% of sPGLs are malignant (71), whereas HNPGLs are usually benign (72).

Malignant HNPGLs usually present with local metastases in cervical lymph nodes or systemic metastases, usually to bones, lung, and liver (69, 70, 72), and occur most frequently in patients with *SDHB* gene mutations (73, 74, 75). In patients with *SDHD* gene mutations, malignant HNPGLs are rare (76, 77). The primary management of patients with malignant HNPGLs should be directed toward complete surgical resection of the primary tumor and regional lymph nodes. Postoperative radiation may be beneficial in slowing the progression of residual disease (72).

Malignant sPGL/PCCs are especially associated with *SDHB*, Myc-associated factor X (*MAX*), and fumarate hydratase (*FH*) mutations (78, 79). There is no effective treatment for malignant sPGL/PCCs. Although debulking of tumor is not evidence based, it may reduce catecholamine-related problems and improve response to further treatment. Up to 60% of malignant sPGL/PCCs show positive MIBG-uptake (80). After resection of ^{123}I -MIBG-positive malignant PGL, postoperative ^{131}I -MIBG treatment for consolidation has been recommended (81). However, considering the frequently encountered long-term stable disease, or very slow progression, and the absence of curative options for metastasized PGL patients, the benefits and side effects of therapeutic interventions should be carefully weighed.

The timing to systemic therapy in these patients has become the subject of debate because, a recent retrospective study in therapy-naïve patients with malignant PGL/PCC has shown that nearly half of patients achieved stable disease at 1 year and that therefore, in symptom-free

patients, a wait-and-scan surveillance policy until imaging proof of progression, preferably by Response Evaluation Criteria in Solid Tumors (RECIST), seems appropriate as first-line treatment (82). A recent systematic review and meta-analysis in MIBG-positive cases have shown that treatment with therapeutic doses of ^{131}I -MIBG resulted in an objective tumor response in 30% of patients and stabilization of disease in 57% of patients (81, 83), and an objective hormonal response in 50% of patients. However, as most studies included patients irrespective of evidence of progressive disease, it cannot be ruled out that stable disease was not merely a therapy effect, but also a reflection of the natural course of the disease. MIBG-negative patients might be treated with combination chemotherapy, of which combination of cyclophosphamide, vincristine, and dacarbazine, the so-called CVD protocol, is the most effective regimen, producing predominantly partial remissions without significant change in overall survival (84, 85). In recent years, treatment with radiolabeled somatostatin analogs such as ^{90}Y -DOTATOC and ^{177}Lu -DOTATOC has also shown its credits in a limited number of patients; Forrer *et al.* (86) reported 13 stable diseases, two mixed responses, and six patients, which remained progressive after treatment of 28 somatostatin receptor-positive patients with metastatic PCC/PGL with DOTATOC, without severe toxicity. In addition, targeted therapies have been introduced in the battle against malignant PCC/PGL, of which especially sunitinib, an oral tyrosine kinase inhibitor, was promising in small series (87). Data from a single open-label phase II trial are currently underway (estimated study completion date: December 2013; Clinicaltrials.gov). Other palliative treatment options are conventional radiotherapy for painful bone metastases and arterial embolization, chemo-embolization, or radiofrequency ablation for liver metastases (88, 89). Catecholamine synthesis inhibitors (α -methyl-para-tyrosine) or α -receptor blockers are useful in reducing catecholamine-related symptoms and signs. Although prognosis in individuals with metastasized PGL cannot be predicted, overall survival is poor with 5-year survival rates of only 20–50% (90, 91).

Hereditary sPGL/PCC

PGLs can occur either sporadically or hereditary, as part of a familial syndrome (55). Inherited disease can be suspected in case of familial antecedents of the disease, multiple primary tumors in the same individual and early age of onset, whereas sporadic PGLs are usually diagnosed in patients older than 40–50 years (92). Until 2000, only

Table 1 Genotype–phenotype correlations in hereditary PCC/PGL.

Syndrome	Gene	HNPGL	sPGL	PCC	Multiple PGL	Bilateral PCC	Malignancy risk	Parent of origin preference
MEN2	<i>RET</i>	Extremely rare	—	++	—	++	+/—	—
VHL	<i>VHL</i>	Rare	+	++	+	++	+	—
NF1	<i>NF1</i>	—	—	+	—	—	+	—
PGL1	<i>SDHD</i>	+++	++	+	+++	+	+	Paternal
PGL2	<i>SDHAF2</i>	+++	—	+	++	—	?	Paternal
PGL3	<i>SDHC</i>	++	+	+/—	+	—	+/—	—
PGL4	<i>SDHB</i>	++	+++	++	++	+	++	—
PGL5	<i>SDHA</i>	+	+	—	—	—	?	—
—	<i>TMEM127</i>	+/—	+/—	+++	+/—	++	+	—
—	<i>MAX</i>	—	—	++	—	++	++?	Paternal
—	<i>FH</i>	+	++	++	++	+	++?	—

+, present; —, absent; HNPGL, head and neck paraganglioma; sPGL, sympathetic paraganglioma; PCC, pheochromocytoma; PGL, paraganglioma; MEN2, multiple endocrine neoplasia type 2; VHL, von Hippel–Lindau disease; NF1, neurofibromatosis type 1; PGL1–5, familial paraganglioma syndrome type 1–5; *SDH*, succinate dehydrogenase; *SDHAF2*, succinate dehydrogenase complex assembly factor 2; *TMEM127*, transmembrane protein 127; *MAX*, Myc-associated factor X; *FH*, fumarate hydratase.

10% of PGLs were associated with hereditary syndromes: von Hippel–Lindau (VHL) disease, multiple endocrine neoplasia type 2, and neurofibromatosis type 1 (NF1), resulting from respectively a germ-line mutation in tumor suppressor gene *VHL* (93), proto-oncogene *RET* (94, 95), and tumor suppressor gene *NF1* (96). PGLs occurring in these syndromes are predominantly (bilateral) PCCs. In the last decade, it has become apparent that about 35% of the apparently sporadic PGLs are due to a germ-line mutation in one of 11 susceptibility genes (97). In addition to the above-mentioned germ-line mutations in *VHL*, *RET*, and *NF1*, germ-line mutations have been found in one of the four subunits (A, B, C, and D) of the *SDH* gene (98, 99, 100, 101), succinate dehydrogenase complex assembly factor 2 (*SDHAF2*), which is responsible for the flavination of the *SDHA* subunit (102), transmembrane protein 127 (*TMEM127*) (103), *MAX* (78), and the recently discovered *FH* (104). Germ-line mutations in *SDHA*, *SDHB*, *SDHC*, *SDHD*, and *SDHAF2* genes are responsible for the occurrence of syndromes named PGL5, PGL4, PGL3, PGL1, and PGL2 respectively. Germ-line mutations in *SDHA* and *C* are associated with HNPGL and sPGL, *SDHAF2* mutations with HNPGL, *SDHD* and *B* with HNPGL, sPGLs and PCC, and *TMEM127* and *MAX* with PCCs (9) (Table 1). *SDHB* mutations are generally associated with a higher malignancy rate than mutations in the other *SDHx* genes. Recent reviews and a meta-analysis of studies involving *SDHB* mutated patients have documented that 17–31% of their tumors were malignant (79, 105). *MAX* and *FH* mutations have also been associated with malignant tumors (78, 104), although data are scarce and involve predominantly index cases.

In addition, germline and/or somatic mutations were reported in EGLN1/prolyl hydroxylase 2 (PHD2) (106), KIF1β (107), IDH1 (108), and hypoxia-induced factor 2 alpha (HIF2α) (109), however, only in a few patients, needing validation in larger series (26). Besides above-mentioned hereditary syndromes, a small fraction of PGLs is associated with other syndromes, including Carney triad and Carney–Stratakis syndrome (110). In addition, other tumors have been documented in *SDH* mutations, such as gastrointestinal stromal tumors (111), renal cell carcinomas (112), and a growth hormone-producing pituitary adenoma (113). Apart from *RET*, which is a proto-oncogene, all the other susceptibility genes for PCC/PGL are tumor suppressor genes.

Hereditary factors and tumorigenesis

PGLs can be divided in two main clusters linked to two different signaling pathways (114). Cluster 1 contains all *VHL*- and *SDHx*-related tumors and is characterized by activation of the hypoxia-angiogenesis pathway in normoxia (115). Consistent with Knudson's two-hit hypothesis for tumorigenesis involving in a tumor suppressor gene, a heterozygous germ-line mutation in an *SDHx* gene is usually associated with somatic loss of the nonmutant allele in the tumor, i.e. loss of heterozygosity. This results in inactivation of *SDH* enzymatic activity and thereby in accumulation of succinate, which acts as an inhibitor of PHD enzymatic activity. PHDs are enzymes that are required for the degradation of HIF. As a consequence, even in the presence of oxygen, HIF cannot be destroyed via proteasome-mediated degradation driven

by VHL protein and is stabilized to induce angiogenesis and tumorigenesis (116, 117). The latter also happens in *VHL* mutations. Interestingly, Letouzé *et al.* (118) have recently described a hypermethylator phenotype in SDH-related PGLs. These tumors accumulate succinate, which inhibits 2-oxoglutarate-dependent histone and DNA demethylase enzymes, resulting in epigenetic silencing, thereby affecting neuroendocrine differentiation. Cluster 2 contains all *RET*-, *NF1*-, *TMEM127*-, and *MAX*-mutated tumors and is associated with abnormal activation of kinase signaling pathways, such as RAS/RAF/MAPK and PI3K/AKT/mTOR, resulting in abnormal cell growth and diminished apoptosis capacity (78, 103, 119, 120, 121, 122). The knowledge of molecular defects in PGLs can be used for development of new effective molecular-targeted therapies.

Genetic testing in PGL/PCC patients and surveillance in mutation carriers

To date, 11 susceptibility PGL genes have been identified. Consequently, the initial 10% of cases classified as genetically determined has increased to ~35%. This percentage is likely to increase, as there are still young patients (with a higher likelihood of a mutation) being classified as sporadic, and patients from PGL families where no mutation is found in one of the 11 susceptibility genes. All familial PGL syndromes have an autosomal-dominant mode of inheritance; interestingly, *SDHD*, *SDHAF2*, and *MAX* are characterized by maternal imprinting, which means paternal transmission only of the disease (9, 123, 124, 125). Up till now, the exact molecular mechanism of maternal imprinting is unknown (126). Because of this phenomenon and incomplete penetrance, especially in *SDHB* mutation carriers (127), many *SDH* mutation carriers have an apparently sporadic presentation. Therefore, a negative family history does not exclude an underlying *SDH* mutation. At present, it is advised to consider genetic testing for an underlying mutation in all PGL/PCC patients, regardless of age and family history (128). Genetic testing algorithms can be made to reduce time and costs. A positive family history for a specific mutation, country of origin, syndromic features, biochemical profile, localization, benign or malignant presentation, and *SDHB* and *SDHA* immunohistochemistry of the tumor tissue (129, 130) may be valuable tools to guide the order of genetic testing (79). In case of HNPGL, *SDHB*, *C*, and *D* may be tested first, if negative, *SDHA*, *AF2*, and *VHL*; in case of concurrent HNPGL and sPGL/PCC *SDHB* and *D*, if negative *VHL*; in case of PCC *RET*, *VHL*, *SDHB*, *D*, if negative *TMEM*

and *MAX*; and in case of malignant sPGL/PCC *SDHB* and *MAX*, if negative *SDHD* and *VHL*. While the majority of patients undergoing SDH mutation analysis will carry missense and nonsense mutations, point mutation-negative patients who carry whole-gene or exon deletions can represent a substantial proportion of all mutations in PGL patient groups. Therefore, deletion screening by multiplex ligation-dependent probe amplification gene deletion analysis should be seriously considered as a follow-up to sequencing in all point mutation-negative patients (131). In the past years, next-generation sequencing (NGS), DNA-sequencing technologies based on massive parallel sequencing, was developed for the genetic screening of PCC/PGL. Although transition to NGS appears inevitable, allowing more rapid and cost-effective mutation detection (132), NGS based screening is still an evolving area with technical limitations, resulting from the presence of pseudogenes or repetitive regions that may result in mapping and alignment errors, to overcome (133).

The finding of a germline mutation in a patient allows for predictive testing of potentially unaffected family members, to be performed in the setting of genetic counseling in an experienced center. Genetic testing can be of great importance for patients and their relatives because it gives the opportunity for early diagnosis in family members of the affected individual (134). Early detection of a familial PGL allows early detection and early treatment with fewer complications of potentially malignant PGLs, especially in *SDHB*, *MAX*, and *FH* mutation carriers (135, 136). However, because up till now only scarce information have been available on age-related penetrance in *SDHx*-, *MAX*-, *TMEM*-, and *FH*-related disease in asymptomatic mutation carriers, genetic testing of family members and subsequent surveillance of mutation carriers remain controversial, especially because tumor screening may cause a significant psychological burden (137). However, with the present nonevidence based knowledge, we recommend regular clinical follow-up in mutation positive carriers (76, 92), except for the children of female mutation carriers of *SDHD*, *SDHAF2*, and *MAX*, because of maternal imprinting. Although there is currently no international consensus regarding follow-up programs, annual biochemical testing, e.g. plasma free MNs and/or urine fractionated MNs, and radiological imaging of neck and/or thorax/abdomen/pelvis every 2–3 years, depending on the mutation, with additional functional imaging in selected cases can be recommended as a surveillance program (76, 138) (Fig. 2). In case of ‘benign’ mutations,

such as SDHD, it can be argued that annual biochemical testing followed by radiological imaging only in case of positive screening is sufficient.

Future perspectives

In the near future, NGS technology is likely to replace conventional sequencing methods, using a stepwise procedure for genetic screening. In addition, new PCC/PGL susceptibility genes are likely to be discovered by whole-genome sequencing. Therapy for malignant/metastatic PCC/PGL is far from satisfying. Continued advances in basic science, diagnostic methods, and imaging techniques will lead to a better understanding of the pathogenesis of these diseases and by unravelling the specific genetic alterations of various PCC/PGL, new molecular targeted therapies will appear as the most promising strategies for the management of patients with metastatic PCC/PGL.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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