Paragangliomas: Clinical Picture

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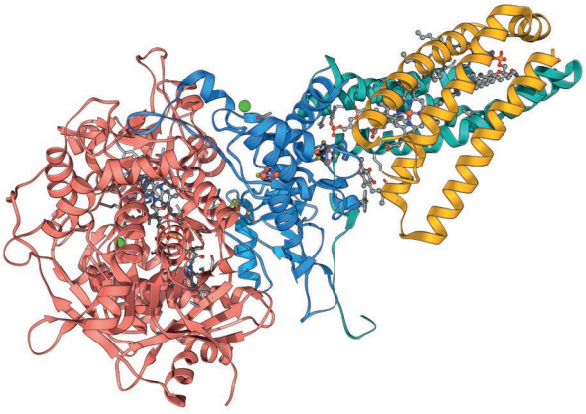
Chapter 1

General introduction



Introduction

Paragangliomas (PGLs) are rare vascular, neuroendocrine tumors of paraganglia. They derive from either sympathetic chromaffin tissue in adrenal (also termed pheochromocytoma (PCC)) and extra-adrenal locations (also termed sympathetic PGL (sPGL)) or from parasympathetic tissue of the head and neck (HNPGL) (Figure 1).[1] The overall estimated incidence of PGLs is 1/300.000.[1-3] From all PGLs, PCCs have the highest relative incidence. In 340 unselected PGL patients, PCC was present in about 73% of the patients, sPGL in 9%, and HNPGL in 20% of the patients.[4,5] PGLs may occur in all ages, with the highest incidence between 40 and 50 years and with no gender differences.[5,6]

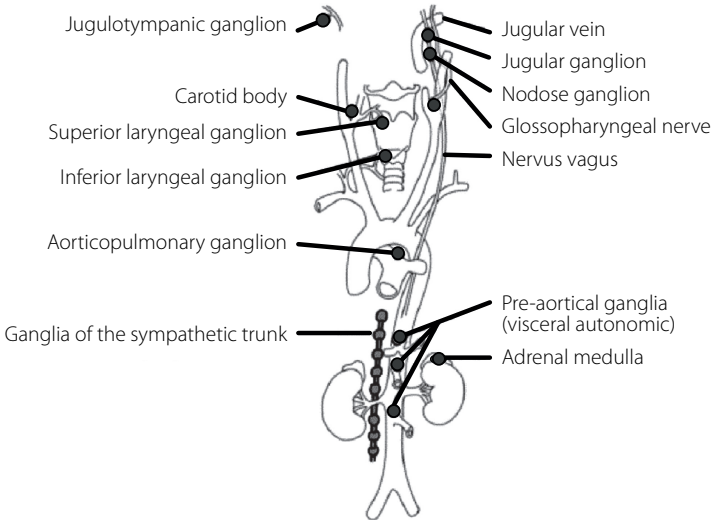


Figure 1. Anatomical distribution of paraganglia. Adapted from Lips *et al.*[7] with permission.

Hereditary syndromes

PGLs can occur spontaneously or as a part of different hereditary tumor syndromes.[8] Before the 21st century, it was thought that 10% of PGL/PCC were genetically determined, caused specifically by germline mutations in the *RET*, *NF1* or *VHL* genes.[3,9-11] After the identification of *SDHD*, *SDHC* and *SDHB* as additional susceptibility genes,[12-14] it became clear that a least 25% of PGL/PCC was inherited.[15] To date, 14 PGL/PCC susceptibility genes have been discovered (*RET*, *NF1*, *VHL*, *SDHD/C/B/A/AF2*, *TMEM127*, *MAX, FH, HRAS, HIF2A/EPAS1* and *KIF1Bβ)*, explaining around one half of cases.[15-20] Mutations in other genes such as *MEN1*, *EGLN1*, *EGLN2*, *MDH2* and *IDH1* have been reported in single cases or families, suggesting that their contribution to the disease is modest.[21-24] In addition, somatic mutations in *ATRX*, *BRAF* and *TP53* have been described, but their role is yet to be established.[25,26]

The *SDHA*, *SDHB*, *SDHC* and *SDHD* genes encode for the four subunits of SDH (mitochondrial complex II), a key respiratory enzyme which links the Krebs cycle and the electron transport chain.[27] The *SDHAF2* gene encodes SDH complex assembly factor 2 (SDHAF2), essential for flavination of the SDHA protein and SDH enzyme activity.[28] Germline mutations in *SDHA*, *SDHB*, *SDHC*, *SDHD*, and *SDHAF2* genes are responsible for the occurrence of syndromes named PGL5, PGL4, PGL3, PGL1, and PGL2, respectively. These various germline mutations have distinct phenotypic effects. *SDHD*-related PGL/PCCs are usually characterized by multiple PGLs, predominantly located in the head and neck region with a low frequency of malignancy. In contrast, *SDHB*-related disease is often diagnosed as a single tumor.[15] In addition, *SDHB* mutation carriers more frequently develop sPGLs, PCC's and malignant disease than carriers with mutations in the other subunits of the *SDH* gene.[29-31] All familial PGL syndromes have an autosomal dominant mode of inheritance. *SDHD*, *SDHAF2* and *MAX* are characterized by paternal transmission of the disease.[15,32-34] Besides the above mentioned hereditary syndromes, a small fraction is associated with other syndromes, including Carney triad, Carney-Stratakis syndrome and, very rarely, MEN1.[22]

Etiology

SDH is located on the inner mitochondrial membrane and is functionally integrated in the mitochondrial respiratory chain and the Krebs cycle. In the respiratory chain, SDH transports electrons to the ubiquinone pool, then to cytochrome *c* of complex III. In the Krebs cyclus, SDH catalyses the oxidation of succinate to fumarate. Thus, two consequences of SDH inactivation are succinate accumulation and increased production of reactive oxygen species.[35] Succinate acts as an inhibitor of prolyl hydroxylase (PHD) enzymatic activity. PHDs are enzymes that are required for the degradation of hypoxia-induced factor (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.[36-38] The increased production of reactive oxygen species has also been suggested to contribute to cellular accumulation of hypoxia-inducible factors.[35,38] Tumors associated with SDH deficiency display notable upregulation of hypoxia-responsive genes. For PGLs associated with mutations in *VHL*, the same signaling pathway is involved.[39]

Clinical presentation

HNPGLs (parasympathetic PGLs) present commonly as a painless, slow growing cervical mass.[1] Many patients are non-symptomatic. Depending on site, however, the tumors may cause symptoms such as pain, tinnitus, hearing disturbances, cranial nerve palsy, hoarseness, and dysphagia.[22] HNPGLs are usually not clinically functional or only produce a low amount of catecholamines. Carotid body tumors (CBTs) are the most common HNPGL. They may, when large and compressive, result in vagal and hypoglossal nerve paralysis.

Vagal body tumors are occasionally accompanied by dysphagia and hoarseness. Tympanic and jugular foramen tumors most commonly present as a vascular middle ear mass, that often present with 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.[40]

The clinical presentation of PCCs and sPGLs is highly variable. They generally produce catecholamines and usually cause hypertension, which may be either paroxysmal or sustained. Typical symptoms are recurring episodes of headache, sweating, and palpitations, however, up to 10% of the patients have only minor or no signs of clinical symptoms and an increasing number of tumors are incidentally found during imaging studies.[41] Symptoms can occur spontaneously or be triggered by direct stimulation of the tumor, physical activity, diagnostic procedures or certain drugs (e.g. metoclopramide).[42]

Depending on the gene that is involved, the clinical characteristics of PCCs, sPGLs and HNPGLs differ (Table 1). Genotype-phenotype correlations can provide important information about the specific characteristics of a genetic syndrome like future tumor risk, anatomical localizations, different hormonal profiles and risks of metastatic disease. Knowing these characteristics might be important to enable optimal genotype-tailored treatment options, follow-up and preventive care.[43]

Treatment

The treatment of choice for PCCs and sPGLs is surgical resection, preferably laparoscopically.[44] In case of a large tumor (in general > 6 cm), with a higher risk of malignancy, conventional laparotomy should be considered. Cortical sparing adrenal surgery should be considered in the management of patients with hereditary pheochromocytoma, especially in patients with VHL or MEN2 hereditary PCC, because of the higher risk of bilateral PCC in these patients.[45] For catecholamine-secreting tumors, pre-operative treatment with an alfa-blocker (phenoxybenzamine or doxazosin) is necessary. Pretreatment reduces perioperative mortality to below 1%.[46]

For HNPGL, a wait-and-scan policy is often advised, because most tumors grow slowly.[47] 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. Treatment options for HNPGLs include surgery, radiotherapy, radiosurgery, radiofrequency ablation or cryoablation.[35] External beam radiotherapy and radiosurgery can result in local tumor control in 79-100%, and sometimes regression by producing fibrosis and vascular sclerosis.[48] 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.

Table 1. Genotype-phenotype correlations due to mutations in 14 susceptibility genes

Gene	Associated syndrome	Year[a]	HNPGL	sPGL	Multiple PGL	Single PCC	Bilateral PCC	Malignancy risk
RET	MEN2	1993	-	-	-	++	++	-
NF1	NF1	1992	-	-	-	+	-	+
VHL	VHL	1995	±	+	+	++	+++	+
SDHD	PGL1	2000	+++	++	+++	+	+	+
SDHC	PGL3	2000	++	+	+	±	-	±
SDHB	PGL4	2001	++	+++	++	++	+	++
SDHA	PGL5	2010	+	+	-	-	-	?
SDHAF2	PGL2	2009	+++	-	++	-	-	?
TMEM127		2010	±	±	±	+++	++	±
MAX		2011	-	-	-	++	++	+
FH		2013	+	++	++	++	+	++?
HIF2A/EPAS1		2012	-?	+	+?	+	?	?
KIF1Bβ		2008	-?	-?	-?	++	+?	?
HRAS		1992	?	-?	-?	++	-?	+?

Abbreviations: *HNPGL* head and neck paraganglioma; *sPGL* sympathetic paraganglioma; *PCC* pheochromocytoma; *PGL* paraganglioma; *MEN2* multiple endocrine neoplasia type 2; *NF1* neurofibromatosis type 1; *VHL* von Hippel Lindau disease; *PGL1-5* familial paraganglioma syndrome type 1-5.

[a] year in which the gene was identified.
+ present; - absent; *?* not known.

Malignant paragangliomas

Although the majority of PGLs are benign, there is a risk of malignant transformation of 10% for PCC and 10-20% for sPGL.[49] Malignant disease is defined as the presence of metastatic lesions at sites where neuroendocrine tissue is normally absent.[50-52] The prognosis in malignant PGL/PCC is known to be poor and treatment remains basically palliative. The overall 5-year survival in patients with malignant PGL/PCC is less than 50%.[49,53,54] Patients with metastatic tumors also have high morbidity rates from excessive catecholamine secretion, hypertension and cardiovascular complications. The primary management of patients with malignant HNPGL should be surgical debulking of tumor tissue and regional lymph nodes. Postoperative radiation may be considered. For patients with malignant PCC/PGL, surgical debulking may also be considered, but the usefulness has not been established.[55] External beam irradiation can be useful in the treatment of local tumor complications. Systemic treatment options include radionuclide therapy with ^{131}I-MIBG or radiolabelled somatostatin analogues,[56] however ^{131}I-MIBG has proved to be the most efficient non-surgical therapeutic modality. Response rates of ^{131}I-MIBG therapy vary considerably, with a great variability in the type and the design of the studies, the administered activity, the schemes of treatment

and the criteria for response assessment. Objective response rates (i.e. stable disease, partial response and complete response) vary from 30-67%.[57-63] A meta-analysis in 1997 performed by Loh *et al.* reported response rates of symptomatic improvement in 76%, anti-tumor response in 30% and hormonal response in 45%.[64]

In MIBG-negative patients, combination chemotherapy of cyclophosphamide, vincristine and dacarbazine (CVD) can be used. This regimen for the treatment of malignant PGL/PCC was introduced in 1985 by Keiser *et al.*[65] Partial remissions and in single cases complete remissions have been reported with this regimen, however, with no significant effect on survival.[65,66]

In the last few years, an increasing number of metastatic NETs have been treated with peptide receptor radionuclide therapy (PRRT) using radiolabelled somatostatin analogues like ^{177}Lutetium (Lu)-DOTA-octreotide and ^{90}Yttrium (Y)-DOTA-lanreotide.[67] Differentiated neuroendocrine cancers frequently express several subtypes of the somatostatin receptor;[67,68] PGL/PCC were found to express predominantly subtypes 2A and 3, and therefore, patients with PGL/PCC are suitable candidates for PRRT.[69] Van Essen *et al*.[70] treated nine PGL/PCC patients with ^{177}Lu-octreotate. None of the patients achieved a complete response on tumour volume; however, a partial response or stable disease was achieved in, respectively, two and four patients. In a study by Imhof *et al*.,[71] 11 patients with PCC and 28 patients with PGL were treated with ^{90}Y-DOTATOC therapy. Seven patients had a partial response after therapy.

Not all patients with malignant PGL/PCC are eligible for MIBG therapy, as it depends on whether the tumours exhibit adequate take up of the radiopharmaceutical after intravenous administration.[72,73] To establish whether a patient is a good candidate for treatment with either ^{131}I-MIBG therapy or PRRT, a diagnostic ^{123}I-/^{131}I- MIBG scintigraphy or ^{111}In-pentetreotide scintigraphy (SRS), respectively, has to be performed in advance. In patients with malignant PGL/PCC with poor ^{123}I-MIBG uptake, but good uptake with SRS, PRRT might be a good alternative treatment for ^{131}I-MIBG therapy.

More recently, studies assessing targeted therapies, such as Sunitinib, have shown promising results in the treatment of malignant PGL.[74] Sunitinib is an oral tyrosine kinase inhibitor with antiangiogenic and antitumor activity. Currently, the published data are limited to only a few case reports and retrospective reports.[74-76]

The prognosis in malignant PGL/PCC is known to be poor and treatment remains basically palliative. The overall 5-year survival in patients with malignant PGL/PCC is less than 50%.[49,53,54,77]

Associated tumors

SDHA, SDHB, SDHC and *SDHD* mutations have also been linked to gastrointestinal stromal tumors [27,78] and renal-cell carcinoma.[79-84] SDH-deficient renal carcinoma has been accepted

as a provisional entity in the 2013 International Society of Urological Pathology Vancouver Classification. Gill *et al.* studied 36 SDH-deficient renal carcinomas and showed that these carcinomas had a strong relationship with *SDH* germline mutation.[85] In addition, pituitary adenomas have been reported to be associated with *SDHA*, *SDHB*, *SDHC* and *SDHD* mutations.[81,86-89] However, other nonparaganglionic tumors may belong to the SDH tumor spectrum, like thyroid tumors.[30,90]

Scope of the present thesis

The aim of the present thesis is to evaluate the clinical characteristics of *SDHx* mutation carriers, to describe the genotype-phenotype correlations, to assess which (nonparaganglionic) tumors can also be linked to *SDHx* mutations and to review various treatment options for malignant PGL/PCC.

In the Netherlands, the majority of hereditary PGLs are caused by *SDHD* and *SDHB* mutations. Founder mutations in *SDHD* are particularly prevalent, but several *SDHB* founder mutations have also been described. The reported penetrance of *SDHB* mutations is 26–75%. In **chapter 2** we describe an extended PGL family with a Dutch founder mutation in *SDHB*, c.201-4429_287-933del, and calculated the penetrance in this kindred.

The prevalence of *SDHB* founder mutations is relatively high in the Netherlands. This gave us the opportunity to perform a nationwide study with 196 *SDHB* germline mutation carriers identified in the Netherlands. In **chapter 3** we describe the genotype-phenotype characteristics of this large Dutch cohort of *SDHB* mutation carriers and assess potential differences in clinical phenotypes related to specific *SDHB* mutations.

SDH mutations have also been linked to nonparaganglionic tumors like gastrointestinal stromal tumors (GIST), renal-cell carcinoma and pituitary adenomas. To explore which nonparaganglionic tumors may belong to the SDH tumor spectrum, we investigated all nonparaganglionic tumors affecting patients included in the Leiden SDH Mutation Carrier Registry. In **chapter 4** we describe which tumors expand the SDH-related tumor spectrum.

PGLs in the head and neck region can arise from the carotid body, vagal body or jugulotympanic tissue (i.e. paraganglioma of the temporal bone). Their location is in close proximity to important neurovascular structures. Therefore, tumor growth may lead to serious morbidity and cranial nerve impairment. Removal of these tumors may lead to carotid sinus nerve impairment. The baroreflex arc has arterial baroreceptors mainly located in the carotid sinuses and aortic arch. Bilateral carotid body tumor resection (bCBR) may thus

result in arterial baroreflex dysfunction. Patients with bCBR are known to have significant lower baroreflex sensitivity compared with controls, i.e. a less marked heart rate response to a given rise or fall in blood pressure. In **chapter 5** we investigated the role of the baroreflex during sleep.

Although the majority of PGLs are benign, there is a risk of malignant transformation of 10% for PCC and 10-20% for sPGL. The prognosis in malignant PGL/PCC is known to be poor and treatment remains basically palliative. There are only a few systemic treatment modalities. Radionuclide therapy is one of these. In **chapter 6** we performed a systematic review and meta-analysis on the effects of radionuclide therapy on malignant PGL. Another treatment option is combination chemotherapy of cyclophosphamide, vincristine and dacarbazine (CVD). The precise effect of CVD chemotherapy for the treatment of malignant PGL/PCC is unclear. In **chapter 7** we performed a systematic review and meta-analysis on the effects of CVD chemotherapy on tumor volume, biochemical response and survival on malignant PGL.

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