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Review

Head and Neck: Paraganglioma: an overview

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Abstract

Review on Head and Neck paragangliomas, with data on clinics, and the genes involved.

Keywords
Head and Neck; paraganglioma; SDHD; SDHAF2; SDHC; SDHB; SDHA; VHL; TMEM127; RET; NF1; MAX

Identity

Other names
chemodectoma
non-chromaffin paraganglioma
glomus tumor
neuroendocrine tumor

Note
The paraganglionic system comprises the adrenal medulla and the extra-adrenal paraganglia. The former gives rise to pheochromocytomas whereas the latter give rise to (extra-adrenal) paragangliomas. The adrenal medulla is the largest collection of paraganglia, and the most common site of paragangliomas (called pheochromocytomas in this location). The extra-adrenal paraganglia are collections of specialized neuroendocrine cells closely associated with large blood vessels, cranial nerves, autonomic nerves and ganglia (Lack, 2007). The paraganglia extend from the base of the skull, on either side of the midline, down to the pelvic floor. They vary in size, being either barely visible under the naked eye (e.g., carotid bodies) or only apparent under light microscopy (e.g., laryngeal paraganglia). Hence, extra-adrenal paragangliomas (PG) may be located anywhere from the upper neck to the pelvic floor (Lack, 2007).
The sympathetic paraganglia are encountered along the axis of the trunk (pre- and para-vertebral sympathetic chains) and in the pelvic floor. The parasympathetic paraganglia are found almost exclusively in the head and neck along the branches of the glossopharyngeal and vagus nerves (Barnes et al., 2005). Most extra-adrenal paragangliomas are encountered above the clavicles. Paragangliomas of the head and neck (HNPG) are found primarily at the bifurcation of the common carotid artery, in the middle ear temporal bone, along the course of the vagus nerve, and, exceptionally, in the orbit, nasal cavity, paranasal sinuses, nasopharynx, larynx, trachea, and thyroid (Barnes et al., 2005). The carotid bodies comprise the largest compact collection of paraganglia in this anatomic distribution, and although uncommon, carotid body paragangliomas (CBP) are the most common paragangliomas of the head and neck region (Lack, 2007; Barnes et al., 2005). Only head and neck paragangliomas will be discussed in this review.

Clinics and pathology

Embryonic origin

The adrenal medulla and the extra-adrenal paraganglia are of neural crest origin (Lack, 2005; Barnes et al., 2005).

Etiology

Familial inheritance (see below) and chronic hypoxia are the only known risk factors in CBP (Barnes et al., 2005; Hensen and Bayley, 2011).

The role of chronic hypoxia in the development of head and neck paraganglioma other than CBP (e.g. laryngeal or jugulotympanic paraganglioma) is debated.
Chronic hypoxia is known to induce paraganglia hyperplasia (Hensen and Bayley, 2011). Since the carotid body plays a central role in oxygen sensing, the latter may be involved in paraganglioma tumorigenesis. Succinate dehydrogenase (SDH) mutations in paraganglial tumors (see below) lead to succinate accumulation resulting in hypoxia-inducible factor 1 (HIF-1) stabilization through inhibition of prolyl hydroxylase-mediated degradation (Hensen and Bayley, 2011, King et al., 2006). This "pseudo-hypoxia" state leads to HIF-induced transcription of genes such as vascular endothelial growth factor (VEGF) and other growth factors.

Epidemiology

Paragangliomas of the head and neck region (HN) are rare, comprising 0.6% of HN tumors and 0.03% of all neoplasms.
The most frequent locations of head and neck paraganglioma are (by decreasing order) carotid body, jugulotympanic and vagal. Paragangliomas more often arise in female patients, usually in the 4th and 5th decades of life (Kimura et al., 2004). Hereditary paragangliomas commonly develop at least 10 years earlier compared to sporadic tumors (Boedeker et al., 2013).

Clinics

Carotid body paraganglioma

Carotid body paraganglioma occurs on average in the fifth decade of life with a roughly equal sex distribution. A female predilection has been noted by some, most notably in series of CBP occurring at high altitude (Lack, 2007). CBP usually presents as a slowly growing asymptomatic mass located deep to the sternocleidomastoid muscle just below the angle of the mandible. It may cause pain, hoarseness, dysphagia, headache, bruit or thrill (Barnes et al., 2005). The patient may present with Horner's syndrome due to involvement of the cervical sympathetic chain and rarely, with carotid sinus syndrome (bradycardia, syncopal episodes). Hypertension due to catecholamine secretion is exceptional. The lesion may be mistaken for an enlarged salivary gland or lymph node, a branchial cleft cyst or rarely, a carotid aneurysm. The tumor may be bilateral, especially in the familial setting. In the latter, about one third of the patients have synchronous or metachronous bilateral tumors; multicentric paragangliomas may occur outside the head and neck region. CBP has been described in Carney's triad (extra-adrenal paraganglioma, gastrointestinal stromal tumor (GIST), and pulmonary chondroma) (Carney, 2009).

Jugulotympanic paraganglioma

Jugulotympanic paraganglioma (JTP) may arise from the glomus jugulare (paraganglia located in the vicinity of the jugular bulb, jugular paraganglioma) or, less frequently, from the glomus tympanicum (paraganglia located near the middle ear surface of the promontory/medial promontory wall of the middle ear, tympanic paraganglioma) (Lack, 2007). However, in large jugulotympanic neoplasms, it may not be possible to precise the exact site of origin. JTP develops in adults in the 5th to 6th decade of life (age range 13-85 years) (Lack, 2007). Solitary JTP arises predominantly in females whereas familial cases occur mostly in men. In one large series of sporadic JTP, the female to male ratio was 6 to 1 with a mean age of 55 years (Brown, 1985).
Tympanic paraganglioma is usually confined to the middle ear cavity. It may cause tinnitus or aural pulsations, and conduction type hearing loss due to involvement of the ossicles. Large tympanic paraganglioma may fill the middle ear cavity. Patients may display ear fullness or pain, otorrhea, chronic otitis media, vertigo/dizziness, and rarely, facial palsy (Lack, 2007; Barnes et al., 2005). On examination, a red vascular or bluish mass may be seen behind a bulging tympanic membrane or protruding through it into the external ear canal. Biopsy of the mass often results in severe bleeding. Similarly, patients with jugular paraganglioma may suffer from conductive type hearing loss, tinnitus, ear pain, facial palsy, and hemorrhage (Lack, 2007; Barnes et al. 2005). The lesion may extend within the petrous bone and intracranially, occasionally simulating a middle cranial fossa or cerebellopontine angle tumor. The jugular foramen syndrome results in paresis of cranial nerves IX to XII due to compression.
JTP (especially hereditary forms) may be bilateral and coexist with CBP, which may also be bilateral, or with pheochromocytoma.

Vagal paraganglioma

Vagal paraganglioma (VP) arises from paraganglia found within or adjacent to the vagus nerve in the vicinity of the ganglion nodosum. VP usually presents as a slowly growing asymptomatic mass at the angle of the mandible or as a bulge in the lateral oropharyngeal wall. Cranial nerve deficits are observed in one third to two thirds of patients at the time of diagnosis. Vagus nerve palsy causes ipsilateral vocal cord dysfunction, hoarseness, or dysphagia (Lack, 2007; Barnes et al., 2005). Large tumors may compress other cranial nerves (IX, XI, and XII) in the jugular foramen resulting in dysphagia, atrophy of the tongue, and shoulder weakness. Ipsilateral Horner's syndrome may occur following cervical sympathetic chain impairment. Functional VP with catecholamine-induced hypertension is uncommon. Handling of such lesion

during surgical removal may induce wide fluctuations in systemic blood pressure.

Laryngeal paraganglioma

Laryngeal paraganglioma (LP) is a rare tumor derived either from the superior or inferior paraganglia of the larynx. The vast majority of LP arises in the supraglottic space and presents as a submucosal mass in the region of the aryepiglottic fold/false vocal cord (Lack, 2007). Only 15% occurs in the subglottis and 3% in the glottis. The right side of the larynx is more often involved than the left (ratio 2.3:1). Median age at diagnosis is 44 years (5-83 years). LP is three times more common in women than in men. The major symptom is hoarseness variably associated with dysphagia, dyspnea, stridor, dysphonia, sore throat, coughing, haemoptysis, foreign body sensation, and otalgia (Lack, 2007; Barnes et al., 2005).

Rare **intrasellar and parasellar paragangliomas** have been reported (Lack, 2007).

Paragangliomas are usually solitary, particularly in adults, but two or more separate tumors may be present. Occasional examples of paragangliomatosis have been reported (Karasov et al., 1982). When multiple, the tumors may appear synchronously or asynchronously. In case of additional paragangliomas, it is usually a carotid body or less frequently, a jugulotympanic tumor.

Imaging

On imaging, paraganglioma appears as a homogeneous, hypervascular, well-defined soft tissue mass. A heterogeneous enhancement may be observed if hemorrhage or thrombosis has occurred. Large tumors may erode the surrounding bone (e.g. labyrinth, jugular foramen). On magnetic resonance imaging (MRI), the tumor appears as a well-defined hypointense mass with areas of signal void on T1-weighted sequences. On T2-weighted images, the signal is usually hyperintense. MRI provides high resolution but is less sensitive compared to CT scan for identifying bone erosion or destruction (Lack, 2007; Barnes et al., 2005). On angiography, there is direct involvement of the carotid bifurcation in CBP with a lyre-like widening of the common artery bifurcation in lateral views. Vagal paragangliomas are located well above the carotid bifurcation and typically displace both external and internal carotid arteries anteromedially (Lack, 2007).

Octreotide scintigraphy helps confirm the neuroendocrine nature of the neoplasm and detect occult paragangliomas. The role of functional imaging procedures in the diagnosis of HNPG has increased in the last 10 to 15 years (Hensen et al., 2013). ^{123}I-meta-iodobenzyl-guanidine (^{123}I-MIBG) or ^{111}In-pentetreotide scintigraphy is useful when in doubt of the diagnosis and in whole-body screening for functional paraganglial tumors, particularly in familial settings (Chen et al., 2010). The ^{18}F-fluorodeoxyglucose-PET (^{18}F-FDG-PET) is also useful in screening for multiple tumors and in detecting metastases (Chen et al., 2010).

Malignant paraganglioma

The diagnosis of malignant paraganglioma usually depends upon the demonstration of metastases to sites such as regional lymph nodes, liver, lung, or bone (i.e. paraganglial cells in non-neuroendocrine tissue). Aggressive local growth, large tumor size, encirclement of carotid vessels, incorporation of nerves, or invasion near the base of the skull also suggests malignancy, although definitive evidence is provided by metastases (Lack, 2007). Most head and neck paragangliomas are benign tumors. Parasympathetic paragangliomas (head and neck region), in contrast to their sympathetic counterparts (trunk, pelvis), are more often familial and less likely to be malignant. Malignant paragangliomas, as their benign counterparts, mainly arise from the carotid body, in the middle ear (jugulotympanic tumors), along the course of the vagus nerve, and exceptionally in the orbit, nasal cavity, paranasal sinuses, nasopharynx, larynx, trachea, and thyroid (Barnes et al., 2005). Malignancy rates up to 10% in HNPG have been reported but those rates vary from study to study. According to one study, 2-13% of CBP are malignant (Barnes and Taylor, 1990). Between 6% and 19% of vagal tumors have been reported to be malignant. For other head and neck locations, malignancy concerns less than 10% of PG (for example, 2 to 4% for JTP) (Lee et al., 2002). The highest malignancy rate was reported for nasal and paranasal PG (24%), followed by vagal (10%), jugulotympanic (5.1%), carotid body (1.41%), and laryngeal PG (1.36%) (Rinaldo et al., 2004). Sporadic (non-familial) CBP are more likely to be malignant than those that are familial (12% versus 2.5%). Malignant paraganglioma may develop in adults at any age (20-80 years old). The median age at first diagnosis in the US National Cancer Data Base was 44 years (Lee et al., 2002). In another series, the mean age was 35 years at diagnosis with 53% of patients being older than 40 (Moskovic et al., 2010). The sex ratio was approximately 1:1 in the cohort reported by Lee et al. (2004). In the series reported by Moskovic et al. (2010), 69% of the patients were males.

Multicentric paragangliomas must be distinguished from true metastases. Most metastases are present at diagnosis or less than 5 years after initial presentation. However, some may be apparent 10 to 20 years after the diagnosis of the primary tumor.

Pathology

Macroscopic examination

Carotid body paraganglioma usually measures between 2 and 6 cm in diameter. It appears firm, rubbery, well circumscribed and surrounded by a

thin fibrous capsule. On cut surface, the appearance is heterogeneous with yellow, tan, pink, red or brown areas. Fibrosis and hemorrhage may be observed. The tumor may encase large blood vessels such as the external carotid. Jugulotympanic paraganglioma often appears as an irregular reddish mass. In jugular paraganglioma, the petrous temporal bone and the middle ear space may be replaced by tumor tissue as far as the tympanic membrane (Lack, 2007; Barnes et al., 2005). Vagal paraganglioma is oval or round and abuts directly onto the skull base. It usually ranges from 2 to 6 cm in diameter and is firm, well circumscribed and surrounded by a thin fibrous capsule. In a few instances, it may be poorly defined and locally infiltrative. It presents with a variegated appearance on cut surface or may be uniformly homogeneous. A portion of one or more large nerves, usually the vagus, is often attached (Lack, 2007; Barnes et al., 2005).

On macroscopic examination, malignant paragangliomas do not significantly differ from benign paragangliomas (except for the occasional presence of lymph node metastases). Malignant paragangliomas typically present as firm, reddish lesions. A fibrous capsule may be seen, but in most instances, the tumor is locally infiltrative. On cut surface, a variegated appearance is noted with yellow-brown, tan-pink, and/or red (hemorrhagic) areas (Lack, 2007; Barnes et al., 2005).

Microscopic examination

Paraganglioma is a neuroendocrine neoplasm composed of chief and sustentacular cells arranged in a characteristic nesting ("Zellballen") pattern (Lack, 2007; Barnes et al., 2005). The chief cells, which are more numerous than the sustentacular cells, display a relatively uniform alveolar arrangement. The sustentacular cells are flattened cells located at the periphery of the Zellballen and are impossible to identify in routinely stained sections. A prominent capillary network is present between the clusters of neoplastic cells. CBP harbors a higher density of chief cells compared to normal carotid body paraganglia. Neoplastic chief cells usually have an abundant, finely granular, eosinophilic cytoplasm containing neurosecretory granules (filled with catecholamines). The sustentacular cells are devoid of such granules. Cell borders may be well-defined with polygonal or angular contours. Vacuolar cytoplasmic changes may be seen. Nuclei may be round to oval with pseudoinclusions. Nuclear pleomorphism, hyperchromasia, and occasional mitotic figures are not indicative of malignancy (Lack, 2007; Barnes et al., 2005). Paraganglioma is often well-demarcated, surrounded by a fibrous capsule. Areas of capsule deficiency should not be regarded as true capsular invasion. Some paragangliomas display areas of hemorrhage or fibrosis. In CBP, the tumor may involve the adventitia of the carotid. Remnants of the normal carotid body may be seen.

Compared to other paragangliomas, JTP tend to more vascular and cell nests are less uniform and frequently smaller. Some JTP present with marked sclerosis (Lack, 2007; Barnes et al., 2005).

Malignant paraganglioma

As already mentioned, a tumor is considered malignant only if there is metastasis to regional lymph nodes or to more distant sites, such as the lungs or bones. There are no accepted histopathological or immunohistochemical criteria for the diagnosis of malignancy in PG. Local compression and erosion of surrounding structures are generally not accepted as a sign of malignancy. Nuclear pleomorphism, mitoses, necrosis, vascular or perineural invasion are not reliable prognostic factors in paragangliomas; the same is true for the Ki-67 proliferation index (Barnes et al., 2005).

Immunohistochemistry

The chief cells express synaptophysin, chromogranin A, and neuron-specific enolase. They do not express cytokeratin or S100 protein. Conversely, sustentacular cells express S100 protein as well as GFAP (glial fibrillary acidic protein). Immunostaining for S100 protein shows elongated, stellate or dendritic sustentacular cells at the periphery of the Zellballen (Lack, 2007; Barnes et al., 2005). According to some, biologically aggressive paragangliomas might have a reduced number of sustentacular cells (and express fewer neuropeptides) compared to benign lesions (Barnes et al., 2005).

n normal paraganglia, the chief cells express SDH subunit B.

In case of an SDH mutation (whatever the SDH subunit involved), as seen in some hereditary paraganglial tumors (see below), the staining for SDHB in neoplastic chief cells will be weaker or abolished. The sustentacular cells will still display positive staining, serving as an internal control. The SDHB staining will be retained in other hereditary tumor syndromes (e.g. von Hippel-Lindau or Multiple Endocrine Neoplasia type 2 (MEN2) syndrome) (see below). Such an immunostaining may guide the geneticist to which gene is involved in the disease pathogenesis.

Differential diagnosis

Differential diagnosis includes carcinoid tumor, medullary thyroid carcinoma, anaplastic carcinoma, metastatic melanoma and renal cell carcinoma (Barnes et al., 2005).

The differential diagnosis of JTP comprises middle ear adenoma/adenomatous neoplasm, meningioma, hemangiopericytoma, and metastatic renal cell carcinoma. Meningioma involving the jugular foramen can mimic the more common JTP. Schwannoma can also involve the jugular foramen (Barnes et al., 2005).

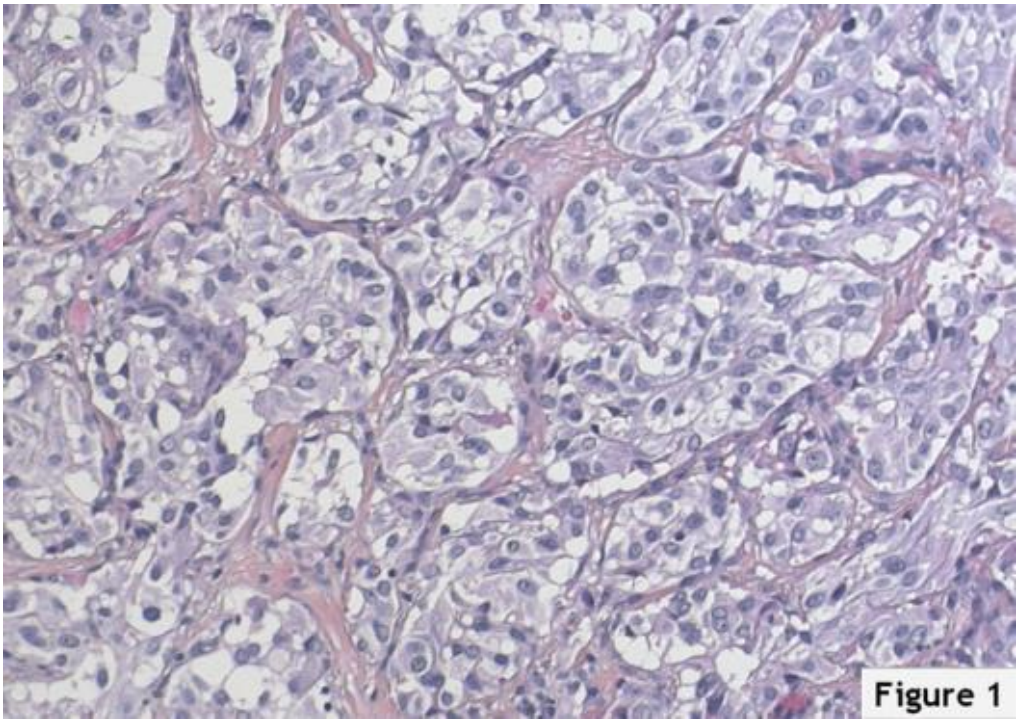

Figure 1: Paraganglioma. Chief cells arranged in the characteristic Zellballen pattern. The cell nests are separated by fibrovascular septa. Hematoxylin and eosin staining (original magnification x200).

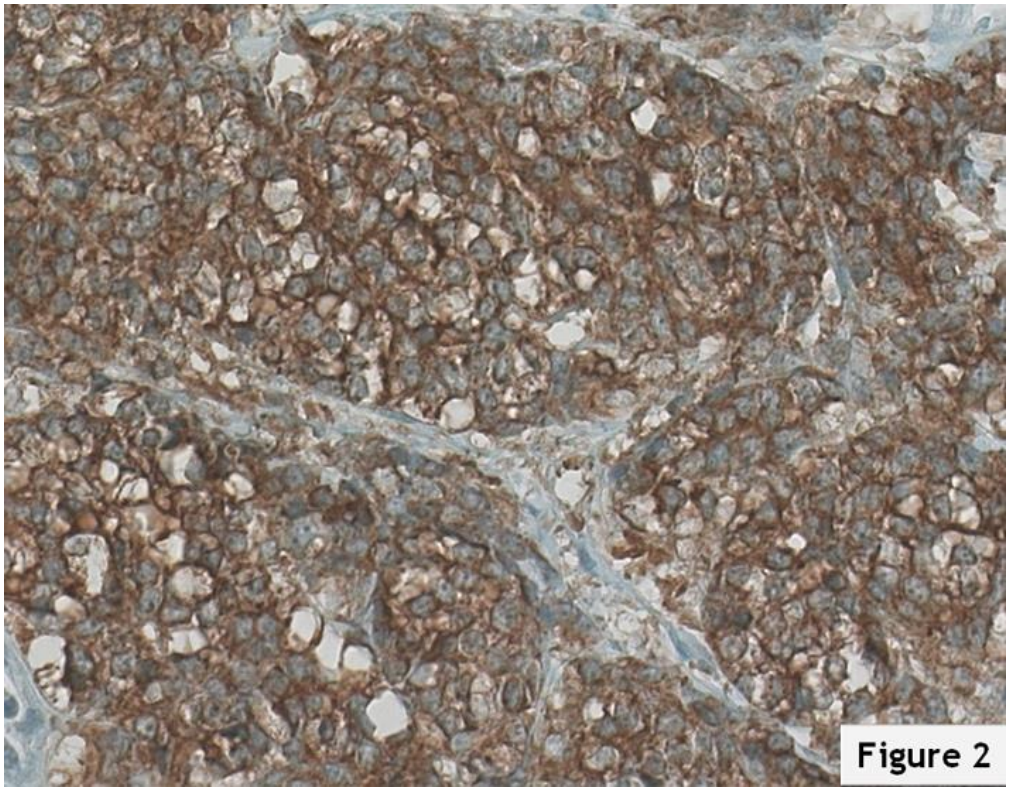

Figure 2: Paraganglioma. Immunostaining for synaptophysin. Strong expression of the neuronal marker by the chief cells (original magnification x200).

Treatment

Paragangliomas are slowly growing tumors. Complete surgical resection is the treatment of choice when feasible (Lee et al., 2002; Moskovic et al., 2010). Tumors involving the base of the skull may require adjuvant radiation therapy. Chemotherapy is largely ineffective. Prolonged follow-up is necessary since the neoplasm may metastasize after a long interval.

In CBP, surgery may require sacrifice of branches of the carotid artery. The recurrence rate is between 0 and 10% and may reflect partial resection and subsequent tumor re-growth. JTP can be locally aggressive neoplasms that destroy bone and extend intracranially, and they may recur (or persist) locally. Regional and distant metastases are uncommon. Radiation therapy, and in some cases surgery, offers a high rate of cure for localized neoplasms. Options for treatment of VP include surgery, radiation therapy, and in selected cases, observation (Moskovic et al., 2010). In most cases, the vagus nerve (and sometimes other cranial nerves) has to be sacrificed. Radiation therapy may be used in case of bilateral tumor. Eight per cent of vagal paragangliomas recurs after surgery, often reflecting inadequate excision.

Because malignant paragangliomas are rare, the survival rate is only available from small case series.

In one study, the 5-year overall survival was 59.5% (Lee et al., 2002). In case of metastases confined to regional lymph nodes, the 5-year survival rate was 76.8% but decreased to 11.8% for patients with distant metastases (Lee et al., 2002). Adjuvant radiation therapy seems the most appropriate treatment in case of metastatic regional lymph nodes (Lee et al., 2002; Moskovic et al., 2010). Bone metastases occur frequently in JTP whereas CBP present with both bone and lung metastases (Moskovic et al., 2010).

Genetics

The classic "rule of 10" for paraganglial tumors (i.e. 10% are malignant, 10% are hereditary and 10% are extra-adrenal) has become inaccurate (Fishbein et al., 2013). The identification of novel causative or susceptibility genes in pheochromocytomas and paragangliomas led to an increase in the rate of familial forms. About one third of all patients with (even apparently sporadic) HNPG are carriers of germline mutations. The rate varies between 24% and 32% (Fishbein et al., 2013) with one study reporting a rate as high as 41% (Burnichon et al., 2009). But the true incidence of familial paragangliomas may be even higher (i.e. 50%). The mode of inheritance is autosomal dominant with, for some syndromes, genomic imprinting (see below) (Boedeker et al., 2013). As a result, no tumor occurs when the gene is inherited from the mother. Paragangliomas may appear in children after paternal transmission even if the father is unaffected. Because of the skipping of generations after maternal transmission, familial forms of the disease are most likely underestimated (Boedeker et al., 2013).

Hereditary paragangliomas of the head and neck (HNPG) have been described in association with mutations of at least 10 different genes (Boedeker et al., 2013; Dahia, 2014).

Mutations of the genes succinate dehydrogenase subunit D (SDHD), succinate dehydrogenase complex assembly factor 2 (SDHAF2, formerly known as SDH5), SDHC, and SDHB are the cause of paraganglioma syndromes (PGL) 1, 2, 3, and 4, respectively.

These genes (as well as the SDHA gene, see below) encode subunits or cofactors of succinate dehydrogenase, which functions as the mitochondrial complex II (Baysal et al., 2000). The latter plays a key role in the mitochondrial respiratory chain as well as the tricarboxylic acid cycle (Boedeker et al., 2013; Dahia, 2014). Complete and selective loss of SDH enzymatic activity is observed in all SDHx-mutant PG regardless of the SDH gene involved. PGL1, 3, and 4 account for 90% of hereditary HNPG.

Succinate dehydrogenase subunit A (SDHA), von Hippel-Lindau (VHL), and transmembrane protein 127 (TMEM127) gene mutations have also been associated with HNPG development (Boedeker et al., 2013; Dahia, 2014).

HNPG in patients with rearranged during transfection (RET), neurofibromatosis type 1 (NF1), and MYC-associated factor X (MAX) gene mutations have been described in rare instances (Boedeker et al., 2013; Dahia, 2014).

Genes involved and proteins

SDHD

Location

11q23.1

Note

Patients with SDHD gene mutations develop HNPG in 91% to 98% of cases (Boedeker et al., 2013). Multiple, synchronous or metachronous, HNPG are a key feature of this syndrome as they develop in most patients (60% to 79%).

Pheochromocytomas and extra-adrenal PG are also observed in 16% to 21% of these patients. The prevalence of malignant paragangliomas reported in PGL1 individuals with manifest disease varied widely, ranging from 0% to 23%.

The pooled incidence for malignant PG was 8% in SDHD mutation carriers (van Hulsteijn et al., 2012). Tumor penetrance is high: 50% by age 31 rising to 86% by age 50 (Neumann et al., 2004). In another study (Hensen et al., 2010), age-related penetrance in patients with PGLA was 54% by age 40 and 87% by age 70. The average range of age at diagnosis of SDHD-mutant tumors was 25 to 38 years (Boedeker et al., 2013). There is also a high prevalence of occult paragangliomas in asymptomatic mutation carriers (Heesterman et al., 2013).

PGL1 families exhibit a peculiar inheritance pattern with a distinct "parent-of-origin dependent effect." (van der Mey et al., 1989). Although SDHD mutations (SDHD gene on chromosome 11q23.1) can be inherited both via the maternal and paternal lines, paraganglial tumors almost never develop after maternal transmission of the mutation (Boedeker et al., 2013). As maternally derived SDHD mutation carriers will still pass the mutation to their offspring in 50% of cases, PGL1 can seem to skip generations, which may in part explain the occurrence of SDHD germline mutations in apparently nonfamilial cases. This virtually exclusive paternal inheritance of disease is consistent with maternal imprinting of the disease gene (van der Mey et al., 1989). The fact that this inheritance pattern is also found in PGL2 families (linked to the SDHAF2 gene, located on 11q13), but not in PGL3 or PGL4 families, suggests that other genes on chromosome 11 are involved. In SDHD-linked paraganglial tumors, the whole maternal copy of chromosome 11 has been found selectively lost (Hensen et al., 2004). Thus, a second paternally imprinted tumor suppressor gene located elsewhere on chromosome 11 may play a decisive role in tumorigenesis, at least in PGL1 and PGL2. In the very few instances of maternal transmission of the disease in PGL1 families, not only was the SDHD or SDHAF2 gene affected but also was the 11p15 region (Pigny et al., 2008; Yeap et al., 2011). This putative tumor suppressor gene has yet to be identified.

SDHAF2

Location

11q12.2

Note

A mutation of SDHAF2 gene on chromosome 11q13 has been identified as the underlying cause of PGL2. PGL2 is also strongly associated with the occurrence of multiple HNPG (70% to 91%), but so far, no extra-adrenal PG, pheochromocytoma, or malignant PG have been described in SDHAF2 mutation carriers (Boedeker et al., 2013). As in PGL1, transmission of PGL2 occurs exclusively via the paternal line. Tumor penetrance is very high (88% to 100%), and the average age at diagnosis is 33-34 years old (Boedeker et al., 2013).

SDHC

Location

1q23.3

Note

SDHC mutations have been detected less frequently than SDHD and SDHB mutations (Neumann et al., 2009). In sharp contrast to patients with PGL1 and PGL4, SDHC mutation carriers mostly present with benign, single HNPG. Multiple HNPG are found in 19% to 31% of patients, and pheochromocytomas, extra-adrenal PG, and malignant PG are seldom reported in PGL3 (Boedeker et al., 2013). The transmission is autosomal dominant. The prevalence for SDHC mutations in two large series of patients with HNPG was 3.6% and 4.3%, respectively (Burnichon et al., 2009; Neumann et al., 2009). Family history is positive in a minority of patients (12% to 25%), suggesting a low tumor penetrance (Neumann et al., 2009). The average age at diagnosis is higher than that observed in the other PGL (range: 38-46 years) (Burnichon et al., 2009).

SDHB

Location

1p36.13

Note

PGL4 is defined by SDHB mutations (SDHB gene on chromosome 1p36). In contrast to SDHD mutation carriers, patients with SDHB mutations frequently develop extra-adrenal PG (52% to 84% cases) and pheochromocytomas (18% to 28% cases), and less frequently HNPG (27% to 31% cases), whereas multifocal HNPG rarely develop (Boedeker et al., 2013). The average age at diagnosis is 30 to 37 years old. The most striking clinical feature of PGL4 is the high percentage of malignant pheochromocytomas and HNPG, ranging from 20.6% to 41% (Neumann et al., 2009; Pasini and Stratakis, 2009). The pooled risk in prevalence studies, depending on the presence of manifest disease, ranged from 13% to 23% in PGL4. The incidence of malignant HNPG and pheochromocytomas is higher in SDHB than in SDHD mutation carriers but may be lower in PGL4 than previously appreciated (van Hulsteijn et al., 2012).

In one study, identification of SDHB mutation was the only risk factor for mortality. The 5-year survival probability was 36% for patients with SDHB mutation versus 67% for patients without SDHB mutation with a median survival time of 42 months for PGL4 patients versus 244 months for SDHB-wild type patients (Amar et al., 2007). SDHB mutations follow an autosomal dominant trait of inheritance. Tumor penetrance is somewhat

lower than that seen in SDHD mutation carriers. The age-related tumor penetrance in PGL4 was in one study 29% at age 30 rising to 45% at age 40 (Benn et al., 2006).
Patients with PGL develop HNPG and pheochromocytomas at a significantly younger age than patients with sporadic paraganglial tumors (Boedeker et al., 2013).
The age at first manifestation of a paraganglial tumor was 36.2 years in the PGL group compared to 50 years in the group with sporadic tumors ($p < 0.0001$) (Myssiorek et al., 2008).
Multiple paraganglial tumors were also significantly more frequent in SDHx mutation carriers.
Finally, patients with PGL also had a significantly higher risk for the development of malignant paraganglial tumors.
PGL1, 3, and 4 are not only associated with paraganglial tumors but also with hereditary renal cell carcinoma (Ricketts et al., 2012; Paik et al., 2014). PGL4 patients have an increased risk of developing papillary thyroid carcinoma, neuroblastoma, and breast cancer (Fishbein and Nathanson, 2012). Pituitary adenomas have been reported in PGL1 syndrome (Xekouki et al., 2012).

VHL

Location
3p25.3

Note
Von Hippel-Lindau syndrome (VHL) is an autosomal dominant tumor syndrome caused by mutations of the VHL gene on chromosome 3p26-25. VHL patients present with hemangioblastomas of the central nervous system, retinal angiomas, renal cell cysts and renal cell carcinomas, pancreatic cysts, as well as pheochromocytomas (Boedeker et al., 2013). In one study, 0.53% of patients with VHL syndrome were found to have HNPG (Boedeker et al., 2009). An association between HNPG and VHL syndrome has also been reported by Gaal et al. (2009).

TMEM127

Location
2q11.2

Note
TMEM127 (Transmembrane protein 127) gene is located on chromosome 2q11. TMEM127 mutation has previously been associated with hereditary pheochromocytoma (Qin et al., 2010). In one study, two out of 48 patients (4.2%) with multiple paragangliomas and no mutation in the SDHB, SDHC, SDHD, RET and VHL genes were found to harbor a TMEM127 mutation (Neumann et al., 2011). Others reported a TMEM127 mutation in 6 out of 642 (0.9%) paraganglioma patients, none of whom had a HNPG (Abermil et al., 2012).

SDHA

Location
5p15.33

Note
The SDHA gene (Succinate dehydrogenase subunit A), located on chromosome 5p15, encodes the major catalytic subunit of the SDH complex.
In Korpershoek et al.'s study, seven of 316 patients (2.2%) with paragangliomas harbored an SDHA mutation.
Two of those 7 mutation carriers presented with HNPG (Korpershoek et al., 2011)

MAX

Location
14q23.3

Note
Recently, germline mutations in the MAX gene (MYC-associated factor X, chromosome 14q23) were identified in 1.12% of patients (out of 1700 individuals) with pheochromocytomas and paragangliomas with no other known mutation (Burnichon et al., 2012).

RET

Location
10q11.21

Note
Multiple endocrine neoplasia type 2 (MEN2) is an autosomal dominant syndrome associated with RET mutations (chromosome 10q11).
So far, HNPG have only been described in 3 patients with MEN2, and as a rule do not develop without other MEN2-associated manifestations (Boedeker et al., 2013).

NF1

Location
17q11.2

Note
Neurofibromatosis type 1 is an autosomal dominant tumor syndrome caused by mutations of the NF1 (neurofibromin 1) gene on chromosome 17q11. NF1 patients present with multiple neurofibromas, café-au-lait spots, axillary freckling, and Lisch nodules of the iris.
One to five percent of NF1 mutation carriers develops pheochromocytomas (Walther et al., 1999).
An HNPG in a NF1 patient has only been described once (Boedeker et al., 2009).
In a cohort of 809 patients with SDHx-wild type HNPG, no NF1 mutation was identified (DeAngelis et al., 1987).

To be noted

Note

The fact that some clearly familial HNPG do not seem associated with any of the known genes makes it very likely that other, yet to be discovered, genes are involved in the development of paraganglial tumors. Candidate genes are kinesin family member 1B (KIF1B) and prolyl hydroxylase domain 2 (PHD2) (Boedeker et al., 2013).

Genetic testing

Approximately one third of all patients with apparently sporadic HNPG suffer from mutations in one of the genes SDHD, SDHB, or SDHC (Boedeker et al. 2013). Recommendations on genetic screening are to test all patients presenting with paraganglioma before age 50, as well as those with malignant, multiple, or familial tumors (Pacak et al., 2007). Neumann et al. (2009) screened 598 patients with apparently sporadic HNPG for mutations of those 3 genes. Mutations were found in 183 patients (30.6%) with 94 SDHD, 63 SDHB, and 26 SDHC gene mutations and no patient presenting with more than one mutation (Neumann et al., 2009). The authors defined six first step predictors: positive family history, previous pheochromocytoma, multiple HNPG, manifestation of first tumor before age 40, and male sex, as well as malignant HNPG (Neumann et al., 2009). A step-by-step approach could be used even though next-generation sequencing will reduce costs and probably allow for up-front screening for all the genes known to be involved in PG (McInerney-Leo et al., 2014). In the mean time, clinical parameters will help to decide which gene(s) should be tested first. Some authors recommend that all patients diagnosed with PG undergo genetic testing (Fishbein et al., 2013). In the study by Fishbein et al. (2013), the patients with mutation in the VHL, NF1, or RET gene did not have a known family history before presentation in 30˜70 % of cases. It is important to refer the patients to the medical genetics department for counseling and deciding which gene(s) to test first. In case of positive family history for paraganglial tumors, the mutation detection rate was 90% (Fishbein et al., 2013).

All mutation carriers should undergo a clinical and radiologic screening after the genetic diagnosis has been established. The only exception may be children of female SDHD and SDHAF2 mutation carriers. In addition to a thorough physical examination, the following procedures should be considered: MRI with contrast medium of the head and neck, the thorax, and the abdomen; catecholamines or metanephrines in plasma or 24-hour urine, and functional imaging in some cases (Boedeker et al., 2013). The percentage of patients with SDHB and SDHD who develop a tumor during the first 2 decades of life is rather high. In the study by Burnichon et al. (2009), 21 of 242 SDHB and SDHD mutation carriers (8.7%) developed a tumor by age 18. The authors therefore suggested beginning examinations in patients with SDHB and SDHD at age 6. Myssiorek et al. (2008) recommend to commence screening at age 10.

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