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Management and follow up of extra–adrenal phaeochromocytoma

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Introduction The prevalence of phaeochromocytoma (PCC) in patients with hypertension is 0.1–0.6% and about 10% of PCCs are detected in extra–adrenal tissue. The diagnosis and therapy of this rare disease detected as a retroperitoneal tumor mass can be difficult for clinicians.

Material and methods A PubMed database was searched for the peer–reviewed articles, the listed articles until Dec 2012 were included. Following key words were used: "extra–adrenal phaeochromocytoma", "paraganglioma", "diagnosis", "therapy", "surgery", "genetic analysis", and "SDH mutation".

Results Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) are first choice imaging tools for PCC (sensitivity 90–100%). For the validation of the diagnosis or follow up, the functional imaging 123I–metaiodobenzylguanidine (MIBG) or Fluorine–18–L–dihydroxyphenylalanine (18F–DOPA) positron emission tomography (excellent specificity and sensitivity of 90–100% in detection of small tumors >1–2 cm) are used. Laparoscopic surgery with complete resection is a safe and a first choice approach. The conversion (about 5%) to direct open operation was needed for large lesions (>8 cm) with the suspicion of malignancy. Currently, there are no histological criteria for distinguishing benign and malignant tumors. The genetic testing (Sanger DNA sequencing) for hereditary syndromes (von Hippel–Lindau, neurofibromatosis, etc.) is used for prediction of malignancy and recurrence. All patients should get individual and risk–adapted genetic analysis and consultation, including family members. The rate of malignancy in ePCC is about 30% (PCC about 5–10%). In patients with proven SDHB germline mutations, higher malignancy rate, multiple PCCs and recurrences are likely. A stringent lifelong clinical follow–up is recommended in these cases. Patients with syndromic hereditary forms should be screened for other often associated neoplasms.

Conclusions New imaging tools and genetic analysis are crucial to improve the diagnosis and prognosis of phaeochromocytoma.

Key Words: extra–adrenal phaeochromocytoma ‹› diagnosis ‹› therapy ‹› surgery ‹› genetic analysis ‹› SDH mutation

INTRODUCTION

The sophisticated classification by the World Health Organization, whose major contributions are from pathologists, classified phaeochromocytoma only as adrenal medullary tumors, and used for all other locations the term paraganglioma. For practical reasons a definition by *Neumann* is applied in the presented review [1]. Here, phaeochromocytoma (PCC) is used for adrenal and extra–adrenal (15%) abdominal, thoracic, and pelvic tumors; these tumors are mostly hormonactive. Paraganglioma (PGL) is exclusively used mainly for the space occupying head and neck tumors [1]. PCC and PGL may arise sporadically or are inherited (about 25%) [1, 2]. The best known hereditary forms of PCC and PGL are von Hippel–Lindau disease (VHL), multiple endocrine neoplasia type 2 (MEN2), and neurofibromatosis type 1 (NF1), associated with other tumor entities. The list of predisposing genes comprises at present 10 genes: *VHL, RET (rearranged during transfection), NF1, succinate dehydrogenase protein complex genes (SDHB, SDHC, SDHD, SDHA, SDHAF2) and* the newly detected *TMEM127, MAX.* Almost one–fourth of pa-

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tients with apparently sporadic phaeochromocytoma may be carriers of mutations [3, 4]. About 10% of the inherited tumors are malignant, depending on the location of the gene mutation [5].

MATERIAL AND METHODS

A PubMed database was searched for the peer–reviewed articles; the listed articles until Dec 2012 were included. Following key words were used: "extra–adrenal phaeochromocytoma", "paraganglioma", "diagnosis", "therapy", "surgery", "genetic analysis", and "*SDH* mutation".

RESULTS

Retroperitoneal phaeochromocytoma is a rare differential diagnosis for malignant renal tumors, which represent a rare disease with the prevalence of 2–8 million patients in a year and about 0.1–0.6% of patients with hypertension. The tumors can occur from early childhood until late in life, with a mean age of 40 years at the time of diagnosis. The once used "rule of tens" stating the frequencies of inherited, malignant, bilateral and extra–adrenal tumors, is out of date. The new diagnostic and genetic methods discount this rule. Higher frequencies for inherited, malignant, bilateral and extra–adrenal tumors were detected depending on the affected gene. PCC can now be referred to as a "10–gene tumor", based on the number of susceptibility genes identified up–to– date [6]. About 25% of patients have an inherited condition associated with different mutations and other tumor entities (*VHL, RET, NF1* and *SDH* genes) [4]. The symptoms are very variable: episodes of palpitation, hypertension, headaches, and profuse sweating are most typical due to the episodes of hormone release.

Biochemical diagnostic

The diagnosis is based on catecholamine excess testing in plasma and urine and the localization of the tumor by imaging. The sensitivity and specificity of available biochemical tests differ considerably, with the highest sensitivity for plasma–free and urinary–fractionated metanephrines (metanephrine and normetanephrine). Metabolism of catecholamines to metanephrines occurs continuously within tumor cells by a process independent of catecholamine release. If metanephrines are not elevated, a phaeochromocytoma is unlikely; if metanephrines are strongly elevated (>3–4x), then the diagnosis is likely and further imaging diagnostics should be performed. The borderline elevations are likely to be false positive and Clonidin suppression should be done [1, 7].

Imaging

The imaging presents no clear criteria for distinguishing renal cell carcinoma from phaeochromocytoma. First choice is MRI (gadolinium contrast) showing a hyperintense mass in T2–phase. The infiltration of local organs and vessels can be better evaluated with MRI than with CT. The other benefit is no need of iodine contrast. Alternatively, a CT scan with contrast can be done with nearly the same sensitivity (90–100%). The benefits of a CT scan are low cost, good availability and high sensitivity (detection of lesion 0.5–1 cm). CT has a low specificity for PCCs, since morphological imaging cannot distinguish these tumors from other types of adrenal masses. Small extra–adrenal tumors can be missed with MRI or CT. It is necessary, especially in hereditary PCCs and PGLs to apply the nuclear medicine procedures for tumor localization, validation and follow up. The radioactive tracers such as ^{131}I, ^{123}I–metaiodobenzylguanidine (MIBG), octreotide (somatostatine) or Fluorine–18–L–dihydroxyphenylalanine (^{18}F–DOPA) positron emission tomography are commonly used [1, 2, 5, 8, 9]. MIBG is a traditional choice of imaging for neuroendocrine tumors since it is more available and can be used for planning the MIBG therapy in metastatic disease, but the resolution and the sensitivity (SPECT) is inferior to DOPA–PET/CT. Excellent specificity and sensitivity of 90–100% for ^{18}F–DOPA in detection of small tumors >1–2 cm was published. A study by Hoegerle et al. showed that ^{18}F–DOPA PET/CT had a higher spatial resolution and a more selective, clearer radiotracer accumulation in PCCs than did ^{123}I–MIBG SPECT [10]. The problem of PET/CT is the lack of availability and high cost, which currently are not reimbursed with medical insurance for this indication. The differential diagnoses of retroperitoneal mass include amongst others hemangioblastoma, sarcoma, renal tumors, non– Hodgkin`s lymphoma and adrenal adenoma. Most frequently, adrenal masses are represented by benign cortical adenomas, which cause a mild hypercortisolism. The criteria for malignancy are established by if there is presence of excessive hormone production and if the tumor size >4–6 cm. Fine–needle aspiration biopsy (FNA) is not useful to distinguish between benign and malignant lesions [1].

Treatment

The treatment options for phaeochromocytoma and the approach of the surgeon have to be discussed and determined. Preoperative patient preparation is essential for a safe surgery. The problem is potential

perioperative hemodynamic instability with tachycardia, arrhythmia, and hypertensive crisis due to the catecholamine secretion. Before the operation a cardiologic checkup with antihypertensive medication, if needed, should be performed. The medication with α–blocker is generally not required. During the operation, the rise of blood pressure can be controlled by f.e. short–acting calcium antagonists and the tachyarrhythmia can be treated with infusion of a short–acting β–blocker. However, perioperative cardiologic complications are rare and patients do not need an intense surveillance. The major postoperative complications are hypotension and hypoglycemia due to the fall of circulating catecholamines. Postoperatively, the antihypertensive medication can be reduced slowly and the blood pressure will normalize regularly a few days after the operation. The perioperative mortality could be reduced over years to less than 3%, mainly due to improved anesthesiological and operative management [1, 7, 11, 12].

The intraoperative aim is a complete surgical resection even if it is often challenging because of the strong vascularization of the tumor and the location near multiple vital blood vessels. The treatment should be performed in specialized centers, otherwise a second opinion is necessary. All patients with phaeochromocytoma, including those at extra–adrenal abdominal, pelvic, and thoracic sites should be initially opted for the endoscopic operation. The results suggest that the endoscopic versus open approach has a shorter hospital stay and less blood loss. Moreover, faster recovery and better cosmetic results were detected after endoscopic surgery [11–14]. The conversion rate of endoscopic to open surgery is about 5%, the reasons being large size of the tumor, malignancy, and bleeding [11, 15]. The open procedure should be reserved for large extra–adrenal tumors with the suspicion of malignancy [15, 16]. The retroperitoneal approach with "no touch technique" seems to be better than transperitonal. The multiple tumors should be removed in a single operation [12]. Walz and colleagues reported on the largest trail (retrospective, non–randomized study) with 144 retroperitoneoscopic or laparoscopic operations for PCCs. The mean tumor size was only 3.5 cm, and the conversion to open surgery occurred only once. The authors also reported excellent results with 11 ePCCs located mostly below the renal vein. Contraindications for the laparoscopic approach include tumors bigger than 8 cm, malignancy, and extreme obesity (BMI>45) [12]. Adrenal–sparing surgery is routine for extra–adrenal tumors, especially in bilateral familial phaeochromocytoma (von Hippel–Lindau, MEN 2) and can be managed endoscopically. The bilateral adrenalectomy has been performed earlier and has lead to a life–long dependency from steroid and mineral corticoid replacement. Postoperatively, catecholamine normalization should be documented and a cortisol deficiency should be excluded if bilateral adrenal cortex–sparing surgery was performed [17].

The prognosis for a completely resected sporadic phaeochromocytoma is excellent. If the tumor is completely removed, the relapse and malignancy risks are low [18, 19]. But about one–third of patients with a hereditary extra–adrenal disease have recurrence [13]. The surgery of recurrent tumor lesions is still controversial, only data with small numbers of patients (n <10) are available. Recurrent lesions need a potentially more intensified and longer surgical preparation. Another problem is probably the increased pCO2 and effects on the blood pressure during laparoscopy [16]. Other studies showed good results of minimal invasive operations of small sized tumor relapse without higher risk of complications [12]. There are no histological criteria to determine a malignant disease. The most common metastatic sites are the skeleton, lungs, liver, and lymph nodes. The treatment is symptomatic or based on palliative radio–chemotherapy (cyclophosphamide, vincristin, dacarbazine) with a 5–year survival of 30–60% [1, 11]. Patients with hereditary disease mutations present higher rates of malignant disease, depending on the location of the mutation.

Genetics

Given the relatively high prevalence of familiar syndromes (about 25%) among patients who present with phaeochromocytoma or paraganglioma, it is useful to identify germline mutations, even in patients without a known family history. Two–thirds of extra–adrenal tumors are associated with one of the hereditary syndromes and have a higher risk of multifocal locations. Other family members should be screened if a germline mutation was detected [1, 5, 7, 20, 21]. The most frequent germline mutations, responsible for familial PCCs, are: the von Hippel–Lindau gene (*VHL*), which causes von Hippel–Lindau syndrome; the *RET* gene, leading to multiple endocrine neoplasia type 2; the neurofibromatosis type 1 gene (*NF1*), which is associated with von Recklinghausen's disease; and the genes encoding the B, C and D subunits of mitochondrial succinate dehydrogenase (*SDHB, SDHC and SDHD*), which are associated with familial paragangliomas and phaeochromocytomas [7, 11] (Table 1).

About 20% of patients with VHL syndrome present with phaeochromocytoma, which are often bilateral and present multifocal abdominal or thoracic locations. Associated tumors are renal clear–cell carci-

Table 1. *Demographic, clinical, and genetic features associated with the six most frequent phaeochromocytoma – and paraganglioma–associated syndromes compared with sporadic tumors*

Syndrome	MEN2	VHL	PGL1	PGL3	PGL4	NF1	Sporadic
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant (father)	Autosom. dominant	Autosomal dominant	Autosomal dominant	No
Gene name	RET	VHL	SDHD	SDHC	SDHB	NF1	No
Gene location	10q11.2	3p25–26	11q23	1q21	1p36	17q11.2	
Age (med., yr)	36 (21–57)	22 (5–67)	27 (5–65)	46 (13–73)	34 (12–66)	41 (14–61)	46 (4–84)
PCC	50%	20–30%	34%	34%	34%	1–3%	
adrenal	97%	92%	86%		43%	100%	93%
extra–adrenal	3%	17%	59%		62%	0%	8%
malignant	3%	4%	0%		32%	12%	4%
associated tumors	MTC; HPT	Eye and CNS Hbl, RCC, islet cell	PTC, GIST	GIST	GIST, RCC	NF, café–au–lait spots, optic pathway, iris hamartomas	

PCC – phaeochromocytoma; HPT – hyperparathyroidism; Hbl – hemangioblastoma; RCC – renal cell carcinoma; PTC – papillary thyroid carcinoma; MTC – medullary thyroid carcinoma; GIST – gastrointestinal stromal tumor. Adapted from other reports [7].

nomas and cysts, primitive neuroectodermal tumor (PNET), central nervous system and retinal hemangioblastomas, pancreatic tumors and cysts, endolymphatical tumors, and epididymal cystadenomas. Malignant disease is rare, but RCC and PNET should be excluded.

In multiple endocrine neoplasia type 2 (5–10%, autosomal–dominant), bilateral tumors occur often (50–80%), while extra–adrenal tumor or malignant disease are very rare. Clinical presentation is not evident because the penetrance of the disease is age dependant. An associated tumor is medullary thyroid carcinoma, which should be operated early [7].

The prevalence of phaeochromocytoma in neurofibromatosis type 1 is relatively rare (1–3%). Because of this, routine screening for the tumor is not generally recommended.

Succinate dehydrogenase or succinate–ubiquinone reductase is the complex II of the mitochondrial respiratory chain located in the mitochondrial matrix. SDH is an enzyme complex composed by four subunits encoded by four nuclear genes (*SDHA, SDHB, SDHC and SDHD*) [20]. Mutations in the four SDH complex subunits and SDHAF2 have been detected in PCC, but frequency, site, and malignancy varies. *SDHA*–mutations give rise to severe neurodegeneration and myopathy, and rare cases of malignancy [22]. An associated protein, SDHAF2, is implicated in flavination of SDHA and is essential for SDH function. There were no metastases found in mutations that were associated with multifocal paraganglioma. [24]. *SDHC*–mutations are rare and are mostly associated with PGL [21]. Mutations of *SDHB and SDHD* genes have been seen in about 5–10% of patients with non–syndromic phaeochromocytoma [23]. *SDHB*–mutations are often associated with extra–adrenal PCC and an increased rate of malignant disease (up to 50%). Rare associated tumors are renal–cell carcinomas; this is not clear for thyroid papillary carcinoma. *SDHD*–mutations that have been inherited from the father develop the disease (often paraganglioma) and those from the mother are disease–free [11, 7, 25]. Life–time tumor risk for *SDH*–mutations seems higher than 70% with variable clinical manifestations depending on the mutated gene [20]. The largest web–based gene specific DNA variant database Leiden Open Variation Database (LOVD) reported three hundred and forty–seven indexed cases as carriers of *SDHB* and two hundred and fifty–three indexed cases as carriers of *SDHD* germline mutations in August 2011. Over a hundred unique DNA variants were described for each of the genes. The mechanism whereby *SDH*–mutations (mostly *SDHB*) predispose to malignancy is unclear. In some instances, the *SDH* subunits apparently behave as tumor suppressor genes, with somatic loss of heterozygosity occurring in neoplastic transformation [21]. Pasini and Stratakis [20] present the results, which strongly suggest the activation of the hypoxia / angiogenesis pathway as a possible mechanism underlying tumor development. In malignant phaeochromocytoma with somatic terminal deletion of 1p (*SDHB*–mutation) the *SDH* activity was abolished with increased expression of the vascular endothelial growth factors VEGF–R1 and VEGF–R2 in endothelial cells.

TMEM127 is a recently detected tumor suppressor gene, which encodes a protein linked to mTOR–sig-

naling. Typically patients that have adrenal phaeochromocytomas (often bilateral), and malignancy is infrequent. The frequency of TMEM127–mutations in PCC is low with about 2% and the need for testing is not clearly defined [26, 27].
New studies identified germline inactivating *MAX*–mutations in PCC and association with malignant outcome and preferential paternal transmission. MAX is a key component of the MYC–MAX–MXD1 network that regulates cell proliferation and differentiation [28].
Genetic information could be potentially useful for the surgeon. In cases that are at high risk for post–surgical complications, especially mediastinal tumors or those at the base of the skull; it could help to decide between watchful waiting or surgical removal [5]. For analysis, a genetic testing and immunohistochemistry should be performed. The exact sensitivity and specificity of the methods vary and have to be determined.

Follow up

Generally, all patients should be followed up every year for at least 10 years after surgery and patients with extra–adrenal or familial pheochromocytoma lifelong. If genetic testing is negative in a patient with phaeochromocytoma, recurrence is very unlikely [11]. Pasini and Stratakis [20] suggest the patients with *SDH*–mutation, a high risk collective and postulate minimum follow–up program (a careful history and physical examination, annual measurement of the blood pressure and urinary catecholamines in addition to bi–annual imaging with CT and/or MRI), starting in the second decade of life (first decade in *SDHB* mutation carriers).

CONCLUSIONS

The management of patients with phaeochromocytoma should be performed by teams of experienced anesthesiologists and surgeons in order to prevent perioperative complications and reduce the morbidity. Endoscopic organ sparing approaches should be favored. Currently there are no histological criteria for distinguishing between benign and malignant tumors. The genetic diagnostics is a crucial tool in following up and counselling the patients and their families. Testing of all genes is expensive and time consuming. For unilateral tumor, age >40 and no familial history, testing is probably not necessary. The monitoring of the patients is based on clinical and biological examination (measurement of urinary catecholamines).
Extra–adrenal phaeochromocytoma is a rare differential diagnosis of patients presenting with a retroperitoneal tumor mass and hypertension. Because of the described pitfalls, it is important consider it and to consult experts early on.

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