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Review

Current concepts of pheochromocytoma

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ABSTRACT

Pheochromocytoma (PCC), a rare neuroendocrine tumor, shows a prevalence ranging between 0.1% and 0.6% in individuals suffering from hypertension. To date, an increasing number of patients with hereditary forms or subclinical PCCs have been diagnosed. We reviewed the main controversies and the most recent updates, especially inheritance genetics and surgical management. According to the "rule of 10", in 1/10 patients with pheochromocytoma it is malignant, in 1/10 of cases the tumor is bilateral, in 1/10 extra-adrenal and in 1/10 familial. Surgical resection, the only curative treatment, carries a high risk of hypertensive crises due to massive catecholamine release. Alpha 1 blocker therapy, alone or in combination with beta blockers, calcium antagonists, and plasma volume expansion, is the most commonly used preoperative treatment protocol. Minimally invasive adrenalectomy (laparoscopic and retroperitoneoscopic) allows earlier mobilization and recovery, reducing the risk of pulmonary infections and thromb-oembolic complications, and is associated with lower morbidity and mortality rates than traditional surgery; it is currently considered the gold standard for the treatment of adrenal tumors $\leq$6 cm in diameter and weighing $<$ 100 g. Genetic testing will increasingly be the key factor in estimating the life-long risk for development of recurrent disease, contralateral disease or malignant dedifferentiation, thus influencing follow-up protocols.

1. Introduction

Pheochromocytoma (PCC) is a rare neuroendocrine tumor originating from the adrenal medulla or from chromaffin cells in sympathetic ganglia, and is most common in women in their 40s and 50s, with an incidence in the United States of 2–8 cases per million per year [1–3]. Surgical resection, the only curative treatment, carries a high risk of hypertensive crises [4,5]. 1/10 patient has a malignant PCC, in 1/10 of cases the tumor is bilateral, in 1/10 extraadrenal and in 1/10 familial [6–9].

It has been shown that minimally invasive adrenalectomy (MA), allowing earlier mobilization and recovery, is associated with lower morbidity and mortality rates than traditional surgery [10]. Improved perioperative management resulted in a significant reduction of complications associated with cardiovascular hemodynamic lability. However, either open or laparoscopic surgical treatment of PCC is still at a high risk of intra-operative blood loss, visceral lesions, and possible adverse cardiovascular events [4,5,11–13,14,15].

Here we review the main controversies and the most recent updates about PCC, especially inheritance genetics and surgical management.

2. Genetics

In the hereditary form, PCC is usually part of more complex clinical syndromes whose causative genes have been identified. The most common hereditary causes of PCC and paraganglioma include

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multiple endocrine neoplasia type 2A and 2B (MEN2A/2B), von Hippel–Lindau syndrome (VHL), neurofibromatosis type 1 (NF1) and familial pheochromocytoma/paraganglioma syndromes.

Multiple Endocrine Neoplasia (MEN) type 2 is characterized by a life-long risk of developing medullary thyroid carcinoma (MTC), which occurs in more than 95% of patients. PCC is associated with two of the MEN2 clinical subtypes, MEN2A and MEN2B, but rarely in familial MTC (FMTC).

MEN2 is an autosomal dominant inherited syndrome with an incidence estimated at 1 in 35,000 individuals. Germline mutations of the REarranged during Transfection (RET) proto-oncogene are responsible for the disease, as recognized nearly 20 years ago. The RET proto-oncogene codes for a receptor tyrosine kinase required for the development of neural-crest derived cells, the urogenital system, and the central and peripheral nervous systems, notably the enteric nervous system [16,17]. The receptor has a large extracellular domain containing a series of cadherin-homology domains and a cysteine-rich region, a transmembrane domain, and an intracellular tyrosine kinase domain that is required for its phosphorylation and downstream signaling. RET activation leads to stimulation of multiple downstream pathways, including mitogen-activated protein kinase and extracellular signal- regulated kinase, phosphoinositide 3-kinase and protein kinase B, signal transducer and activator of transcription 3, proto-oncogene tyrosine-protein kinase Src1 and focal adhesion kinase, all of which promote cell growth, proliferation, survival, and/or differentiation [18]. MEN2-associated mutations are located in exons 10, 11 or 13–16 of the gene; mutations in exons 5 and 8 have also but rarely been reported. The large majority is dominant and heterozygous, cause amino acid substitutions either in the extracellular or the tyrosine-kinase domain of the receptor resulting into its constitutive activation in the absence of ligands and co-receptors.

Strong genotype–phenotype correlations exist such that the codon where the mutation occurs can be used to predict the MEN2 subtype, the risk for a PCC, the occurrence of hyperparathyroidism and the age of onset and aggressiveness for MTC. PCC occurs in up to 50% of individuals with MEN2A and MEN2B bearing mutation of codon 634 (MEN2A) and codon 918 (MEN2B) respectively. It has not been found in kindreds with mutations at codons 532–534, 630, 777 and 912. Because PCC is more commonly seen in association with the high-risk mutations for MTC, its presence may imply a more aggressive thyroid tumor. PCC tends to develop after MTC is identified; however, there are well-documented examples of MEN2-related PCCs presenting before MTC as the initial manifestation of the syndrome. Less than 3% of cases of apparently sporadic PCCs occurring before the age of 50 years are due to germline mutations of the RET proto-oncogene [19]. MEN2-associated PCCs are often detected by routine biochemical screening or for symptoms such as hypertension, palpitations, headache, tachycardia or sweating. The typical age of onset is the third decade of life, 10–20 years earlier than the typical age of sporadic PCC development. The American Thyroid Association has provided the management guidelines for the initial diagnosis, therapeutic intervention and long-term follow-up based on patients' genotype and the current understanding of the natural history of the disease associated with each RET mutation [20].

Von Hippel–Lindau (VHL), a common cause of hereditary PCC, should be one of the first syndromes to be considered, particularly if the patient is very young or if the tumor has noradrenergic catecholamine secretion. Overall, VHL accounts for approximately 11% of apparently sporadic PCCs, most of them benign and intra-adrenal, although extra-adrenal paragangliomas (PGLs) and malignant tumors can occur [21,22]. Von Hippel–Lindau syndrome is an autosomal dominant disease characterized by PCC, renal cancers, retinal and/or cerebellar hemangioblastomas, cystic as well as neuroendocrine pancreatic tumors. VHL is classified into two main types based on the risk of PCC. Type 1 is characterized by a low risk, whereas type 2 by a high risk of PCC. This latter is further subdivided based on the risk of renal cell carcinoma: type 2A is associated with a low risk while type 2B with a high risk of renal cell carcinoma. Finally, type 2C is defined as a PCC occurring without other manifestations of the disease. The VHL gene is located on chromosome 3p25, and its primary function is the regulation of hypoxia-induced cell proliferation and angiogenesis. It acts as a tumor suppressor gene and, in fact, the syndrome is caused by inactivating germline mutations. In addition, most VHL-associated pancreatic endocrine tumors display loss-of-heterozygosity (LOH) of the VHL gene in the somatic tissue, supporting its role as suppressor in tumor development.

Neurofibromatosis type 1 (NF1) is also associated with hereditary PCC. Patients with NF1 present manifestations that are obvious at physical examination, most commonly including café-au-lait macules, neurofibromas and axillary and inguinal freckling by the time they are at risk of developing a PCC [23]. Genetic testing is thus generally not necessary to establish a correct NF1 diagnosis. NF1 is a large gene of 60 exons, located on chromosome 17q11.2 coding for the protein neurofibromin. The gene, discovered in 1990, has one of the highest spontaneous mutation rates in the human genome, including missense, nonsense, and splice- site mutations as well as intragenic deletions (indels) and chromosomal rearrangements. NF1 is mainly expressed in the nervous system, where it represses cell proliferation by promoting the conversion of RAS into its inactive form, thereby inhibiting the oncogenic RAS/RAF/MAPK signaling cascade [24]. Neurofibromin also inhibits the PI3K/AKT/mTOR pathway via RAS suppression (Max), implying that NF1 functions as a classical tumor suppressor gene. PCC only rarely develops in NF1 and tends to behave as a sporadic pheochromocytoma. The average age of onset is in the fourth decade, but it can also occur in childhood and examples of multigenerational PCCs have been reported. Most NF1-associated PCCs produce norepinephrine and noradrenergic symptomatology; however, 22% have no symptoms related to excessive catecholamine secretion. Approximately 11–12% of such tumors are malignant, 10% are bilateral and over 94% have an intra-adrenal localization [25].

During the last decade, mutations in the genes coding for the different subunits of the succinate dehydrogenase (SDH) complex have been linked to Hereditary pheochromocytoma/paraganglioma (PCC/PGL) syndromes. Subsequent genetic screenings have revealed that about 30% of PCCs and PGLs are caused by such germline mutations [26]. In addition, several novel susceptibility genes, such as transmembrane protein 127 (TMEM127) and MYC-associated factor X (MAX), have been added to the list. These newly identified predisposing genes seem, at first glance, to have entirely different functions but in spite of this, malfunction of their different gene products can give rise to clinically and histologically undistinguishable tumors. Nevertheless, some clinical features may be quite different: for instance, patients with SDHB mutations have considerably a higher risk of malignancy than many other PCC/PGL patients. Familial paragangliomatosis is associated with germline mutations of the genes coding for the various subunits of the succinate dehydrogenase (SDH), a mitochondrial enzyme complex consisting of four subunits: SDHA, SDHB, SDHC and SDHD, all of which are encoded by nuclear genes [27]. The enzyme, also known as mitochondrial complex II, is involved in the tricarboxylic acid cycle, where it catalyzes the oxidation of succinate to fumarate, and in the respiratory electron transfer chain, where it transfers electrons to coenzyme Q. SDHA is located on chromosome 5p15.33, consists of 15 exons and codes for a protein that functions as a part of the enzyme catalytic core and contains the binding site for succinate. The other part of the catalytic domain, which also forms