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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

an interface with the membrane anchor, is encoded by SDHB, a gene of eight exons located on chromosome 1p36.13. SDHC on chromosome 1q23.3 and SDHD on chromosome 11q23.1 contain six and four exons, respectively, and code for two hydrophobic proteins that anchor the complex to the mitochondrial inner membrane. The link between SDH and neuroendocrine tumors was first established in the year 2000, when germline mutations in SDHD were discovered in patients with familial PGLs [28]. Germline mutations in the SDH genes give rise to the familial PCC/PGL syndrome, sometimes only referred to as familial PGL. The syndrome can be divided into PGL1, PGL2, PGL3, and PGL4, caused by mutations in SDHD, SDHAF2, SDHC, and SDHB, respectively, all inherited in an autosomal dominant manner with varying penetrance. The prevalence of the PCC/PGL syndrome is unknown, but it is estimated to be 1:50,000 to 1:20,000, the majority represented by PGL1 and PGL4. Apart from PCCs and PGLs, SDHB mutations have been associated with renal cell carcinoma. Mutations in SDHB, SDHC, and SDHD can give rise to the Carney-Stratakis syndrome, characterized by the dyad PGLs and gastrointestinal stromal tumors (GISTs). Very recently, SDHA mutations have been reported in two patients with GISTs but without PGLs. SDHD mutations (PGL1) most frequently predispose to parasympathetic, often multifocal PGLs, but also to sympathetic PGLs and PCCs. Several studies have gathered information about tumor characteristics in patients with PCC/PGL syndrome [29,30].

The transmembrane protein 127 (TMEM127) gene has been found mutated in hereditary PCCs and identified as a PCC susceptibility locus in 2005. However, no specific syndrome has been linked to TMEM127. Other tumors, including MTC, breast cancer, and myelodysplasia, have been identified in carriers of TMEM127 mutations, but a causal relationship between the tumors and the mutations remains to be established [31]. A clear family history is reported in only a fourth of the patients suggesting an incomplete penetrance; in a single family, the penetrance of PCC of 64% by the age of 55 years is also reported. TMEM127 is formed by four exons located at 2q11.2 coding for a transmembrane protein that acts as a negative regulator of mechanistic target of rapamycin, formerly mammalian target of rapamycin (mTOR), thus linking a critical signaling pathway for cell proliferation and cell death to the initiation and development of PCC. Both missense and nonsense germline mutations of TMEM127 have been reported along with LOH of the gene in tumors of all tested mutation carriers, supporting the notion that it functions as a tumor suppressor through the classical two- hit model. Among 990 patients with PCC or PGL, negative for RET, VHL, and SDHB/C/D mutations, TMEM127 mutations are detected in 20 cases (2.0%), all of which have PCC. In another study only one additional PCC patient with a TMEM127 mutation has been found while no TMEM127 mutations are detected in 129 sympathetic and 60 parasympathetic PGLs [32]. In a recent study, germline missense variants are reported in two out of 48 patients with multiple PGLs, one of which also displays bilateral PCC [33]. Summarizing the 23 reported patients, all but one (96%) has PCC and 39% have bilateral PCCs, two (9%) have PGL, one of which sympathetic and the other multiple parasympathetic PGLs. The mean age at presentation is 43 years, and one patient (4%) shows a malignant tumor.

MYC-associated factor X (MAX) mutations segregate with the disease in families with PCC, but no specific syndrome has been described yet. A paternal origin of the mutated allele in the investigated cases, together with the absence of PCC in individuals who inherit a mutated allele from their mother, may suggest a paternal transmission of the disease similar to PGL1 (SDHD) and PGL2 (SDHAF2). Comino-Mendez et al. [34] have reported 12 PCC patients with MAX mutations, three of which identified with the exome next generation sequencing and four of which as probands' relatives. The remaining five have been found in a subsequent screening of 59 PCC patients lacking mutations in other known susceptibility genes but suspected to have hereditary disease. Of the 12 patients, eight (67%) have bilateral PCC and the mean age at presentation is 32 years. Notably, 25% of the patients present metastasis at diagnosis, suggesting that MAX mutations are associated with a high risk of malignancy.

MAX is a gene of five exons, located on chromosome 14q23.3 that codes for a transcription factor, MAX, belonging to the basic helix-loop-helix leucine zipper (bHLHZip) family. It plays an important role in the regulation of cell proliferation, differentiation and death as a part of the MYC/MAX/MXD1 network [35,36]. Some tumors can grow in the absence of MYC-MAX dimers and imply that MAX can function as a tumor suppressor, a role that has most recently confirmed, as germline MAX mutations are discovered in PCC patients by next-generation exome sequencing [35].

3. Preoperative management

α-adrenergic receptor antagonists, calcium channel blockers and metyrosine are the most used drugs as preoperative protocol therapy. Selective α1 blockers have been introduced to avoid the main side and delayed therapeutic effects of phenoxybenzamine, a non-selective alpha blocker. Before alpha blockers were introduced in the 1950s, perioperative mortality, currently limited to 0–6% [10,37,38], ranged between 24% and 50% [39,40].

The first drug therapy suggested was a combination of beta blockers and phenoxybenzamine. In order to avoid its side effects, selective alpha 1 blockers were used: firstly prazosin then terazosin and doxazosin, which are currently widely used. Doxazosin, a competitive selective alpha 1 antagonist, lipophilic with high bioavailability and relatively long-acting, is administered once daily [41,42]. P. Tauzin-Fin and C. Prys-Roberts reported a better blood pressure (BP) and heart rate (HR) control with doxazosin than with phenoxybenzamine, observing that an effective preoperative adrenergic blockade does not prevent hypertensive crises but neutralizes catecholamine effects [41,42]. Reports regarding preoperative drug therapy outcomes show contradictory data. L.B. Perry, C.A. Deoreo and A.R. Boutros did not observe any difference between mortality rates of treated and untreated patients [43–45]. On the contrary, J.C. Ulchaker, in 113 patients who underwent surgery between 1977 and 1994, reported no mortality among preoperatively treated patients, but more severe cardiovascular complications, concluding that preoperative alpha adrenergic blockade is not essential [5], according to K.A. Newell [46]. However, J. Steinsapir reports 2 deaths among patients who underwent surgery without preoperative therapy [47]. Y. Zhu, in a recent series of 67 cases, reported more stable perioperative hemodynamic changes in patients pretreated with doxazosin, irrespective of phenoxybenzamine [48]. Also T.N. Weingarten concluded that non selective α-blockade produces a better decrease of intra-operative hypertension, but it is followed by a longer hypotension, requiring a greater use of vasopressors [49]. Calcium antagonists, inhibiting calcium- dependent norepinephrine release, are also very effective in the preoperative blood pressure and peripheral vascular resistance control [50].

Alpha 1 blocker therapy, alone or in combination with beta blockers, calcium antagonists, and plasma volume expansion, is therefore the most commonly used treatment protocol, as confirmed by van der Horst-Schrivers [2]. In our experience, a treatment with doxazosin (2–10 mg daily) was administered for at least 2 weeks preoperatively, in more than 60 cases of LA. Selective alpha 1 blockers resulted very effective in BP and HR control. Preoperative adrenergic blockade did not guarantee hemodynamic stability, but allowed an optimal pharmacological control of hypertensive crises, in absence of major adverse cardiovascular events [51,52].

Table 1
Results of minimally invasive adrenalectomy in patients with pheocrhomocytomas.

Authors	Patients (number)	Operative time (minutes)	Blood loss (ml)	Conversion (%)	Morbidity (%)	Mortality (%)
M. Gagner ('96)	23	230	–	0	22	0
M.K. Walz ('02)	52	116 ± 52	100	0	23	0
D.E. Jaroszewski ('03)	47	140	80	11	4.8	0
A.W. Kim ('04)	26	191	276	4	23	0
K.W. Kercher ('05)	80	169	97	0	7.5	0
Y. Naya ('05)	23	192.7	130	4.34	0	0
A. Toniato ('07)	40	78	100	3	2.5	0
M.J. Mellon ('08)	11	181.4	–	1.4	10	0
K.A. Perry ('09) PCC<6 cm	22	189	68	9.1	13.6	0
K.A. Perry ('09) PCC>6 cm	8	212	130	37.5	12.5	0
G.Y. Meyer-Rochow ('09)	36	183	–	2.7	13.9	0
L.N. Castilho ('09)	24	126	–	0	16.7	0
P. Nau ('10)	33	142	–	12.1	6	0
W.T. Shen ('12)	102	186	–	3	13.7	0
Y.M. Carter ('12)	25	–	–	0	0	0
Conzo ('12)	60	165	130	5	8.3	0

4. Surgery

PCC surgery remains hazardous and multidisciplinary high volume centres may obtain the best results. MA, since first description by M. Gagner in 1992 (laparoscopic) and lately by M.K. Walz in 1995 (retroperitoneoscopic), associated with a lower morbidity rate, shorter hospital stay, and a more rapid recovery than "open" surgery, is currently considered the gold standard for the treatment of adrenal tumors ≤6 cm in diameter and weighing < 100 g. Most benefits are well known [5,51–53]. M.M. Murphy, in a recent review, reported statistically significant lower morbidity and mortality rates than traditional surgery, due to reduced postoperative pulmonary infections and thrombo-embolic complications [10]. Even though improved perioperative management, advances in anesthesiology and surgery have allowed a significant reduction in mortality and morbidity, PCC surgery is still a challenge, especially for large lesions, because of the extensive vascularization, the difficulties in mobilization and dissection of the adrenal gland, the tenacious adhesions to adjacent structures. Moreover, the risk of malignancy and of local recurrence, were considered in the past as a contraindication to laparoscopic treatment of PCC >6 cm [53]. Nevertheless, according to R. Bellantone, PCC >6 cm in diameter becomes malignant less frequently than other adrenal lesions of the same size do, and probably size cannot itself be an absolute contraindication for LA [54]. Currently, indications to LA for lesions >6 cm is still a matter of debate, and experienced endocrine surgeons are divided between supporters [3,13,38,54] and detractors [55,56]. In our experience, LA was safe for most patients with PCC, even in selected cases >6 cm without preoperative suspicion of malignancy. Laparoscopic surgery was associated with acceptable morbidity rate, similar to those previously reported for other adrenal diseases [57,58]. We observed a higher incidence of intraoperative hypertensive crises and of conversion to open surgery in PCC larger than 6 cm, but statistically significant differences were never reported. Blood loss, operative time and incidence of complications did not seem to be affected by PCC size. So we propose to treat cautiously even PCC 6–8 cm in diameter by LA, if great care is adopted to avoid capsular disruption, and a prompt conversion is considered in case of technical difficulties to reduce patient risks [13,51,59–63]. Literature data confirm the effectiveness and safety of MA (Table 1).

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Author contribution

Giovanni Conzo: Participate substantially in conception, design, and execution of the study and in the acquisition of data, analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript and in final approval of the version to be submitted.

Daniela Pasquali: Participate substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting of the manuscript.

Vittorio Colantuoni: Participate substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting of the manuscript.

Luisa Circelli: Participate substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting of the manuscript.

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Claudio Gambardella: Participate substantially in conception, design, and execution of the study and in the acquisition of data, analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Nicola Avenia: Participate substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting of the manuscript.

Luigi Santini: Participate substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript and in final approval of the version to be submitted.

Antonio Agostino Sinisi: Participate substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting of the manuscript.

Conflicts of interest

All authors declare that they have no financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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