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Pheochromocytoma - diagnosis and treatment, review of literature

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Abstract:

Introduction:

Pheochromocytomas are rare tumors originating from the adrenal medulla, which can occur sporadically or as part of hereditary syndromes. Many patients with chromaffin tumors harbor genetic mutations, typically inherited in an autosomal dominant manner, hence genetic testing is recommended for all patients. Symptoms can result from both excessive catecholamine production and the mass effect of the tumor. Diagnosis is confirmed by elevated levels of metanephrines or normetanephrines in the plasma or urine. Radiological imaging aids in tumor localization and assessment of potential local invasion or metastasis. Preoperative preparation of all patients involves the use of α-receptor blockers and/or other medications to control arterial hypertension, arrhythmias, and fluid volume. Surgery remains the treatment of choice, with lifelong follow-up recommended.

Objective:

The review article aims to provide an overview of chromaffin tumor pathology, their etiology, discuss diagnostic possibilities, and indicate therapeutic options for patients.

Materials and Methods:

A summary of reports available in medical publications and scientific studies found in databases such as PubMed, CrossRef, Google Scholar, as well as relevant textbooks.

Results:

Chromaffin tumors are rare but dangerous for patients; adequate pharmacological preparation for surgery, which is usually necessary, is extremely important.

Conclusions:

The main role is to establish the correct diagnosis, or even suggest and conduct diagnostic tests towards a chromaffin tumor. Patient management involves controlling blood pressure, appropriate premedication, and surgical intervention. After such treatment, patients require continuous monitoring to detect any potential disease recurrence.

Keywords: epidemiology, genetics, medication, pathology, pheochromocytoma, radiology, surgery, symptoms, treatment

World Health Organization (WHO) defines paragangliomas as neuroendocrine tumors arising from the neural crest tissue. They most commonly occur in the adrenal glands and are called pheochromocytomas, while those outside the adrenal glands are called extra-adrenal paragangliomas. [8]

Pheochromocytoma, a chromaffin tumor, is a neoplasm originating from chromaffin cells. It is located in the adrenal glands, and patients' symptoms result from excessive production and release of catecholamines from this tumor. Treatment requires surgical resection of the tumor, but adequate pharmacological preparation of the patient is necessary before the procedure. Chromaffin tumors belong to the group of tumors secreting catecholamines together with paragangliomas (PPGL - pheochromocytoma and paraganglioma), occurring independently of gender, and are most commonly diagnosed in patients in the 4th and 5th decades of life. Patients most commonly die due to heart attack, stroke, or rhythm disorders. [1]

Chromaffin tumors mostly occur as sporadic cases (about 60%), less commonly familial (up to 40%), with germinal mutations underlying these changes. These changes are usually located in the adrenal glands, unilaterally in 90% of cases, with a predominance of involvement of the right adrenal gland. Bilateral occurrence of chromaffin tumors is more common in children (35%) and in cases with familial predisposition (24%). These tumors more often have a benign character.

- - Genetic syndromes in which chromaffin tumors occur include:
- - Multiple endocrine neoplasia type 2A and 2B - MEN2A and MEN2B
- - Von Hippel-Lindau disease - VHL
- - Neurofibromatosis type 1 - NF-1

- - Pheochromocytoma and paraganglioma syndrome - PGL
- - Beckwith-Wiedemann syndrome

Multiple endocrine neoplasia type 2A and 2B:

MEN 2, inherited in an autosomal dominant manner, results from a mutation in the RET proto-oncogene (chromosome 10). MEN 2A occurs much more frequently (90%) than MEN 2B (10%).

MEN 2A (also known as Sipple's syndrome) leads to the development of medullary thyroid carcinoma (95-100%) in patients, primary parathyroid insufficiency (35%), and pheochromocytoma (averaging ~50%, but ranging from 6% to 100%). Additionally, patients have a higher propensity for developing flat warts and Hirschsprung's disease. Pheochromocytoma develops in middle-aged individuals and may occur without arterial hypertension. Individuals from families affected by MEN 2A should undergo genetic testing for the RET proto-oncogene mutation before the age of 6. In the presence of the mutation, patients undergo prophylactic thyroidectomy and are closely monitored for the development of pheochromocytoma and parathyroid overactivity [1,15,18].

MEN 2B, occurring much less frequently than MEN 2A, is characterized by the development of more aggressive forms of pheochromocytoma or medullary thyroid carcinoma. Additionally, patients exhibit a marfanoid habitus, mucosal neuromas (around the eyes and oral cavity), and intestinal ganglioneuromas. Similar to MEN 2A, patients with a family history of MEN 2B should undergo genetic testing for RET proto-oncogene mutations. Upon confirmation, thyroidectomy is also recommended, and the patient remains under constant specialized observation [1,18].

Von Hippel-Lindau disease:

Von Hippel-Lindau disease (VHL) represents a syndrome of genetic predisposition to tumors, characterized by autosomal dominant inheritance. The pathogenesis of this condition is associated with germinal mutations in the VHL gene. Clinically and pathologically relevant changes include embryonic vascular tumors (hemangioblastomas) within the cerebellum and spinal cord (CNS-HB), retinal hemangioblastomas (R-HB), clear cell renal carcinoma (CC-RCC), pheochromocytomas, neuroendocrine tumors (PNET), and endolymphatic sac tumors (ELST). Additionally, cysts and cystadenomas may occur in the kidneys, pancreas, epididymis, and broad ligament of the uterus, although they typically remain asymptomatic and do not pose a significant clinical problem. Tumors in patients with VHL disease typically manifest multifocally, bilaterally, and develop at an early age. The diagnosis of VHL disease

is based on familial-clinical criteria and/or analysis of VHL gene mutation carrier status. Von Hippel-Lindau disease is divided into types 1 and 2. Pheochromocytomas occur in patients with VHL type 2 [1,3,16,18].

Neurofibromatosis type 1:

Neurofibromatosis type 1 (NF-1, von Recklinghausen disease) is an autosomal dominantly inherited disorder characterized by variable individual and age-related expression. Half of the cases are caused by de novo mutations and are not associated with inheritance. The symptoms are attributed to mutations in the NF-1 tumor suppressor gene. This change leads to a loss of neurofibromin production by the body, which in turn predisposes to tumor formation. Typical symptoms of neurofibromatosis type 1 include café-au-lait skin changes, both subcutaneous and involving the nerve sheaths of cranial and spinal nerves, Lisch nodules (iris hamartoma), and skeletal abnormalities. The incidence of diagnosed chromaffin tumors correlated with NF-1 is only 5%, however, in patients with NF-1 accompanied by hypertension, the likelihood of pheochromocytoma presence ranges from 20% to 50%. Therefore, annual screening for pheochromocytoma is recommended for patients diagnosed with NF-1 and concomitant hypertension. Additionally, all NF-1 patients should be screened for pheochromocytoma before pregnancy or surgical procedures [1,4,18].

Pheochromocytoma and Paraganglioma Syndrome (PGL):

Due to the association of the adrenal medulla with the paraganglia of the autonomic nervous system, pheochromocytoma can be interpreted as a particular case of paraganglioma. Analyses of the genotype-phenotype relationship have shown significant differences in the clinical manifestation of familial paraganglioma syndromes. Five types of these syndromes are distinguished, ranging from PGL1 to PGL5. Their main cause are mutations in genes encoding subunits of succinate dehydrogenase (SDH). Characteristic of PGL1 (SDHD) is the occurrence of head and neck paragangliomas, which typically have a benign course. On the other hand, PGLA syndrome (SDHB) is characterized by excessive secretion of noradrenaline and dopamine, often occurring at a young age (usually around 30 years), with tumors located outside the adrenal glands and often exhibiting malignant features. In the case of PGL3 (SDHC) and PGL2 (SDHAF2) syndromes, head and neck paragangliomas are observed, less frequently chromaffin tumors. Additionally, additional genes have been identified whose mutations are associated with the occurrence of pheochromocytomas and paragangliomas, such as SDHA (PGL5 syndrome), TMEM127, MAX, and others. Approximately 12% of all patients with paragangliomas and chromaffin tumors have germinal mutations in the SDH gene [1,5,18].

Beckwith-Wiedemann Syndrome:

Beckwith-Wiedemann Syndrome (BWS) is a genetic pathology characterized by excessive body growth, predisposition to tumorigenesis, and congenital defects. The etiopathogenesis of

BWS results from various epigenetic and/or genetic factors that cause disturbances in gene expression on chromosome 11. Although the disease most commonly arises from de novo changes (in 85% of cases), familial inheritance cases have also been registered (in 15% of cases). Chromaffin tumors diagnosed in patients with BWS most commonly occur bilaterally [1,6,18].

Table 1. Genetic Syndromes Predisposing to Pheochromocytoma

Genetic Syndrome	Components	Gene
MEN 2A	Medullary thyroid carcinoma, pheochromocytoma, parathyroid overactivity, flat warts, Hirschsprung's disease	RET
Men 2B	Medullary thyroid carcinoma, pheochromocytoma, ganglioneuromas, marfanoid habitus	RET
Von Hippel-Lindau Disease	Retinal hemangioblastomas, pheochromocytoma, renal carcinoma, pancreatic cysts, epididymal cystadenomas, CNS hemangioblastomas	VHL
Neurofibromatosis Type 1	Café-au-lait spots, neurofibromas, iris hamartomas, skeletal abnormalities, pheochromocytoma	NF1
Pheochromocytoma and Paraganglioma Syndrome	Paragangliomas, pheochromocytoma	SDHB/SDHD

Based on: Zgliczyński W, Prejbisz A, Janusiewicz A, Pęczkowska M, Janusiewicz W. Wielka interna Endokrynologia tom II, 2020

Physiology of Pheochromocytoma

Pheochromocytomas may be hormonally inactive; however, in the majority of cases, they cause the secretion of catecholamines. Compared to a healthy adrenal gland, their production by a pheochromocytoma can be up to 27 times higher. Additionally, in chromaffin tumors, the concentration of noradrenaline is usually higher than adrenaline (unlike in a healthy adrenal gland), although this relationship does not always occur. Hypertensive attacks in patients can be caused by hemorrhage into the tumor or its compression due to injury or even torso torsion. In addition to the secretion of catecholamines and their metabolites, pheochromocytomas can secrete a variety of other peptide substances, for example: neuropeptide Y, calcitonin-related peptide – which can cause hypercalcemia, or adrenocorticotropic hormone (ACTH) causing Cushing's disease. Small tumors release much more catecholamines into the bloodstream compared to large tumors because large tumors undergo catecholamine catabolism, resulting in milder clinical symptoms. A "typical" pheochromocytoma has a diameter of about 4.5 cm and weighs around 100 g, but the range of sizes can include tumors from microscopic changes to those weighing 3600 g. [1,5,7]

Table 2. Substances Secreted by Pheochromocytomas

Adrenaline	Chromogranin A
Noradrenaline	Cytokines
Metanephrine	Erythropoetin
Normetanephrine	Growth hormone
Dopamine	Neuropeptide Y
ACTH	Parathyroid hormone related peptide
Atrial natriuretic peptide	Renin
Calcytonin	Serotonin

Based on: David G. Gardner, Endokrynologia ogólna i kliniczna Greenspana tom I, 2011

Impact of catecholamines on the body

Primarily, a significant impact of catecholamines on the circulatory system is observed. If the tumor secretes more noradrenaline (with higher affinity to alpha adrenergic receptors) compared to adrenaline, it leads to increased alpha-adrenergic stimulation – vasoconstriction and increased cardiac contractility, resulting in increased blood pressure, hyperglycemia (through intensified glycogenolysis, gluconeogenesis, and insulin secretion inhibition).

Stimulation of beta-adrenergic receptors mainly causes increased myocardial contractility and heart rate. Noradrenaline strongly stimulates alpha receptors, while adrenaline equally affects both alpha and beta receptors. [5,17,19]

Clinical picture

The diversity of clinical symptoms associated with pheochromocytomas (PPGL) and the possibility of their co-occurrence with other genetic disorders lead to diagnostic challenges. Due to the rich symptomatology, pheochromocytomas are sometimes referred to as "great mimickers." Clinical diversity mainly results from the type of catecholamines secreted - adrenaline or noradrenaline. Studies conducted under the PMT program have shown that patients with PPGL are characterized by more frequent occurrence of tachycardia and lower body mass index compared to individuals in whom PPGL has been ruled out. Additionally, patients with PPGL have been observed to have increased blood glucose levels. Chromaffin tumors secreting interleukin 6 may cause fever, which does not respond to antibiotic treatment, and an increase in inflammatory marker levels in serum. Symptoms of arterial hypertension in PPGL may vary depending on the pace of catecholamine synthesis, the number, and sensitivity of adrenergic receptors in the tumor. In clinical practice, PPGL should be suspected in patients with arterial hypertension characterized by large blood pressure fluctuations, alternating pressure increases, orthostatic hypotension, or tachycardia after changing body position, significant heart rate variability, and a paradoxical reaction to some antihypertensive drugs. Arterial hypertension in the course of PPGL may be difficult to control pharmacologically, leading to treatment-resistant hypertension. Patients with PPGL may also experience complications of the cardiovascular system, such as acute heart failure associated with the action of catecholamines, acute coronary syndrome, or stroke. Paroxysmal symptoms such as sweating, abdominal pain, vomiting, and arterial pressure fluctuations may be characteristic of PPGL. The frequency and intensity of attacks may gradually increase, and attacks may be triggered by various factors such as changes in body position, physical exertion, or stress. In some cases, chromaffin tumors may secrete sufficient amounts of ACTH to stimulate excessive cortisol production, leading to the development of Cushing's syndrome. It is also worth noting that chromaffin tumors may lead to various complications, such as metastases to various organs, including the skull, spine, or lungs, significantly worsening the patient's prognosis. About 15% of chromaffin tumors are malignant. These tumors are characterized by active secretion and may cause recurrence of hypertension and other symptoms even many years after successful surgical removal. Metastases are usually metabolically active and may cause various symptoms, depending on the target site. Metastases to the skull are particularly dangerous, as they can lead to neurological complications such as headaches, visual disturbances, or paralysis. Additionally, malignant tumors may metastasize to the spine, leading to back pain and neurological syndromes associated with compression of the spinal cord. In the case of chromaffin tumors associated with MEN 2 syndrome or von Hippel-Lindau disease, patients are often asymptomatic,

making early diagnosis difficult. However, in patients with malignant chromaffin tumors or metastases to other organs, intensification of symptoms is usually observed, which may have significant clinical implications for prognosis and therapy planning. [1,2,5,7,9,17,19]

Table 3. Frequency of PPGl Symptoms

Symptom	**Frequency [%]**
Hypertension	95
Heart palpitations	65
Excessive sweating	55
Weakness	51
Headaches	46
Anxiety	37
Paleness	37
Tremors	33
Nausea/vomiting	26
Blushing	21
Constipation	17

Wielka interna – Endokrynologia tom II. Wojciech Zgliczyński, 2020r, s 74-80

Pheochromocytoma, although rare during pregnancy, poses challenges for both the mother and the fetus. Its occurrence is estimated to be between 1 in 15,000 to 1 in 54,000 pregnancies, and if unrecognized and untreated, it can lead to maternal and fetal mortality rates reaching as high as 40–50%. Research suggests that the overall mortality rate for mothers with a chromaffin tumor during pregnancy is about 9.8%, and for fetuses, it is 16%. Hypertension developing before the 20th week of pregnancy should raise suspicion of the presence of a pheochromocytoma. Symptoms such as episodic hypertension, severe headaches, sweating, palpitations, and orthostatic hypotension, are characteristic of this condition. Diagnosis relies on biochemical tests similar to those used in non-pregnant patients. Radiological studies are only applied after obtaining positive results from biochemical tests. Safe imaging modalities during pregnancy include MRI and ultrasonography. Surgery is necessary, and its preparation and execution should follow the standards applied to non-pregnant patients. Performing the operation in the second trimester is recommended, considered the safest due to the risk of miscarriage in the first trimester. Laparoscopic adrenalectomy is a safe surgical method during pregnancy. Recommendations suggest avoiding vaginal delivery in women with pheochromocytoma during pregnancy, which is an important aspect of caring for patients with

this rare disease. Additionally, preoperative α-adrenergic blockers may reduce the risk of maternal and fetal mortality [7].

Laboratory Diagnosis

The laboratory diagnosis of pheochromocytoma (PPGL) and related extra-adrenal chromaffin tumors is based on the measurement of various substances, including metoxykatecholamines, catecholamines, and markers such as chromogranin A (CgA). Traditionally, 24-hour urine tests were used to measure catecholamines, total and fractionated metanephrines, and vanillylmandelic acid (VMA). Currently, the preferred diagnostic method is the measurement of fractionated metanephrines in blood or urine collected over 24 hours. An exception is made for small tumors (<1 cm), which do not release catecholamines, and exceptional cases of tumors producing only dopamine. Methylcatecholamines, such as normetanephrine and metanephrine, are catecholamine metabolites measurable in the patient's blood and urine. Their levels are elevated in the presence of chromaffin tumors. Catecholamines, such as noradrenaline and adrenaline, are inactivated by catechol-O-methyltransferase (COMT), leading to the formation of methylcatecholamines. These substances circulate in the serum at low concentrations and are excreted from the body through urine. Blood tests should be performed in the supine position approximately 15–20 minutes after inserting the intravenous catheter. Patients should fast overnight and abstain from food, coffee, caffeine-containing beverages, strenuous physical exertion, or smoking cigarettes for at least 8–12 hours before the test. Additionally, avoiding paracetamol intake for 5 days before the test is recommended, as it may affect the results of normetanephrine measurement in serum. A blood metanephrine concentration exceeding four times the upper reference limit is associated with nearly 100% probability of chromaffin tumor presence. A significant elevation in metanephrine suggests excessive adrenaline production, locating tumors in the adrenal medulla. In cases where patients have blood metanephrine levels above the upper reference limit but less than four times above this limit, the clonidine suppression test may be useful. This test has very high sensitivity and specificity (100% and 96%, respectively) for diagnosing tumors in such situations. In cases of suspected tumors producing only dopamine, which are rare, dopamine and its metabolite 3-methoxytyramine levels are not routinely measured in blood or urine. However, in cases of metastatic disease, these tests may be useful because metastatic tissue often does not exhibit mature enzymes necessary for catecholamine synthesis. Elevated 3-methoxytyramine levels in blood have been proposed as a highly sensitive marker of malignant tumors compared to tests for dopamine levels in blood/urine. Depending on the patient's age, there are specific reference values for metanephrine, normetanephrine, and 3-methoxytyramine in blood, established based on research conducted by Lenders and Eisenhofer (2017). The method recommended by the European Society of Endocrinology for patient testing is liquid chromatography with mass or electrochemical detection

In summary, measuring metoxykatecholamines and other biomarkers such as CgA is an important tool in the diagnosis of chromaffin tumors. Their analysis allows for effective

disease identification and monitoring, enabling prompt initiation of appropriate treatment and improving patient prognosis. [1,5,7,10]

Imaging

Imaging plays a crucial role in diagnosing chromaffin tumors, confirming the diagnosis in cases of positive or borderline biochemical test results, and precisely determining the location, size, and optimal therapeutic approach. Additionally, it enables the assessment of metastases and multifocal disease, which is important for determining the stage of disease advancement. After treatment initiation, imaging allows for the assessment of treatment response and monitoring for potential relapses, which is crucial for long-term patient care. Imaging methods include both anatomical techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (USG), as well as functional imaging, which utilizes physiological processes or receptor-specific substances. [8]

Computed Tomography and Magnetic Resonance Imaging

In the radiological diagnosis of chromaffin tumors, magnetic resonance imaging (MRI) and computed tomography (CT) play an extremely important role, enabling a detailed morphological analysis and characterization of tumors and their surroundings.

MRI allows for precise localization of the adrenal glands and assessment of anatomical structures in their vicinity. For comprehensive assessment, both T1-weighted images, which enable tissue signal evaluation, and T2-weighted images, which allow for identification of potential pathological changes, are recommended. An important diagnostic feature of chromaffin tumors on T2-weighted images is their bright signal, similar to cerebrospinal fluid, facilitating their identification. Additionally, gradient imaging techniques can help distinguish chromaffin tumors from other adrenal lesions.

In the case of CT, almost all chromaffin tumors exhibit more than 10 Hounsfield units (HU) on unenhanced images, which is an important diagnostic feature. Contrast-enhanced venous CT imaging may also be useful due to characteristic differences in enhancement between chromaffin tumors and other adrenal lesions.

In both cases, it is important to consider the size of the tumor and any morphological features such as the presence of necrosis or central fibrous tissue. In cases of suspected metastasis or tumor progression, further investigations such as biopsy or resection may be necessary.

In summary, both MRI and CT are indispensable tools in the diagnosis of chromaffin tumors, allowing for a precise assessment of tumor characteristics and its location, which is crucial for further diagnostic and therapeutic management. [7,8,9,10]

Ultrasonography

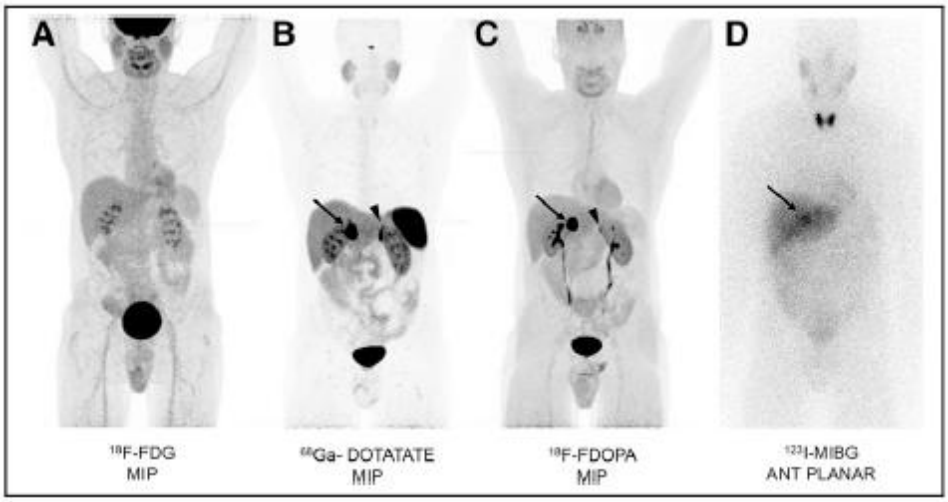
During abdominal ultrasound examination, a chromaffin tumor typically manifests as a well-demarcated lesion. In the case of larger chromaffin tumors, internal necrotic-hemorrhagic cysts are often observed, leading to an uneven appearance of the tumor. Ultrasonography through body walls is most sensitive in individuals with a slim body build, where up to 85% of chromaffin tumors can be identified. However, ultrasound examination is not specific because it does not allow differentiation between a chromaffin tumor and an adrenal cortical adenoma or an upper pole kidney tumor. Similarly, a left adrenal chromaffin tumor may be misinterpreted as a pancreatic tail tumor, and a right adrenal chromaffin tumor as a liver tumor. Ultrasonography may be the preferred imaging modality in the initial evaluation of chromaffinomas in pregnant women, infants, and small children, although it is inferior to magnetic resonance imaging. Additionally, ultrasonography is used in identifying and monitoring neck paragangliomas. For endoscopic ultrasonography using a linear probe inserted into the stomach or duodenum, small adrenal chromaffin tumors, lymphatic metastases, and local recurrences can be detected. In the context of pelvic and bladder paragangliomas, transvaginal ultrasonography is very useful in their identification and monitoring. [1,20]

Scintigraphy with metaiodobenzylguanidine (MIBG)

MIBG, derived from guanidine, exhibits similarity to norepinephrine and is actively transported by the norepinephrine transporter system to the adrenal medulla cells, where it selectively accumulates in neurosecretory granules. Unlike norepinephrine, MIBG is characterized by low affinity for catecholamine receptors and undergoes no metabolic transformations. Scintigraphy using 123I-MIBG or 131I-MIBG is useful in diagnosing adrenal chromaffin tumors, identifying occult paragangliomas, and confirming the diagnosis of paraganglioma or pheochromocytoma in certain extra-adrenal tumors. Imaging with MIBG also allows for the detection of metastases. MIBG uptake may occur even in clinically non-functional tumors. Radiolabeled MIBG (131I/123I-MIBG, iobenguane) binds to norepinephrine transporters, which are internalized and transported to secretory granules via vesicular monoamine transporters. Guidelines have been published regarding patient preparation, administration, pharmacokinetics, biodistribution, and dosimetry of imaging procedures for chromaffin tumors or paragangliomas using 123I/131I-MIBG. Before administering MIBG, it is necessary to ensure that the patient has not taken any medications that may interfere with its action. Due to the potential release of free 123I/131I, thyroid protection is recommended, typically using a saturated solution of potassium iodide 2–24 hours before MIBG administration and continuing for several days afterward. Imaging with 123I-MIBG is preferred, while 131I-MIBG is used for dosimetry before therapy or for documenting biodistribution after therapy. After MIBG administration, blood clearance occurs rapidly, with over 80% excreted from the body within 2–5 days, mainly through the kidneys. Normal biodistribution includes uptake in the liver, lungs, heart, spleen, and salivary glands (Figure 1). The adrenal glands are often visible, and in the absence of abnormalities on CT, uptake at or below the level of the liver is considered physiological. A meta-analysis

demonstrated high sensitivity of 123I-MIBG at 96% in patients with non-metastatic chromaffin tumors or paragangliomas and 79% in patients with metastatic chromaffin tumors or paragangliomas. Recent studies, including a larger number of paraganglioma cases, have generally shown lower sensitivity in detecting MIBG, especially in patients with hereditary chromaffin tumors or paragangliomas. Typically, the sensitivity of 123I-MIBG is higher for detecting chromaffin tumors than for detecting paragangliomas, at 88% and 67%, respectively. MIBG sensitivity in patients with SDHx is low. With the introduction of newer radiopharmaceuticals, the role of radiolabeled MIBG in imaging chromaffin tumors/paragangliomas has diminished to a screening test for 131I-MIBG therapy. [1,5,7,8,9,10,17,20]

Figure 1.



Carrasquillo JA, Chen CC, Jha A, Ling A, Lin FI, Pryma DA, Pacak K. Imaging of Pheochromocytoma and Paraganglioma. J Nucl Med. 2021 Aug 1;62(8):1033-1042.

Positron Emission Tomography

Functional imaging (FI) studies of pheochromocytomas (PHEOs) utilize various PET ligands, such as (18)F-fluorodopamine [(18)F-FDA], (18)F-fluorodihydroxyphenylalanine [(18)F-FDOPA], and (18)F-fluoro-2-deoxy-D-glucose [(18)F-FDG]. PET (18)F-FDA and PET (18)F-FDOPA are most commonly used
in identifying lesions not detected by anatomical imaging, providing an additional benefit in cases of malignant PHEO. Studies have shown that PET (18)F-FDA was particularly effective in identifying metastases in patients with metastatic PHEO, which is crucial for therapy planning and disease progress monitoring. PET imaging offers higher resolution and signal-to-noise ratio compared to SPECT, making it a promising method in PHEO diagnosis. However, limitations
in the availability and production of PET ligands hinder their widespread clinical application.

Despite these challenges, research on new PET ligands for PHEO is ongoing to improve the diagnosis and management of this rare disease. [1,5,7,8,9,10,17,20]

Differential Diagnosis

(Giannini et al. 1978, Manger 2009)

The differential diagnosis of pheochromocytomas includes:

- Anxiety disorders, including benzodiazepine withdrawal syndrome.
- Paragangliomas.
- von Hippel-Lindau disease.
- Primary hypertension.
- Hyperthyroidism.
- Insulinoma.
- Mercury poisoning.
- Paroxysmal supraventricular arrhythmias.
- Renovascular hypertension.
- Carcinoid syndrome.
- Baroreceptor failure.
- Orthostatic tachycardia syndrome.
- Sleep apnea.
- Renal failure.
- Pseudopheochromocytoma (Severe paroxysmal hypertension)

Cases from 10 to 15 may exhibit elevated levels of catecholamines and their metabolites in blood and urine.

Preoperative Preparation for Surgery

To minimize the risks associated with PHEO surgery, appropriate preoperative treatment aimed at blocking the effects of catecholamines for at least 10–14 days before the procedure is necessary, with some authors even suggesting up to 21 days. Adequate preoperative α-blockade has been shown to reduce the number of perioperative complications to less than 3%. The three perioperative phases most associated with hypertensive episodes are tracheal intubation, creation of pneumoperitoneum (in laparoscopic adrenalectomy), and manipulation of the adrenal gland. Significant hypotensive episodes may also occur and are associated with a sudden drop in catecholamine levels after tumor removal. Preoperative α-blockade is the standard procedure to prevent intraoperative hemodynamic instability during PHEO resection.

Oral phentolamine is no longer used for preoperative preparation; it is reserved only for emergent cases in the form of intravenous administration. The most commonly used α-adrenergic blockers for preoperative preparation are phenoxybenzamine (pheno) and selective competitive α1-adrenergic blockers, such as terazosin and doxazosin (dox), which have a shorter half-life and reduce the risk of postoperative hypotension. Side effects of α1-adrenergic blockers include orthostatic hypotension, syncope, and nasal congestion. Calcium channel blockers (CCBs) are an alternative to phentolamine for preoperative blockade of catecholamine-induced vasospasm. CCBs also reduce the risk of intraoperative hemodynamic instability, but it is controversial whether one method is superior. A β-adrenergic blocker may be used preoperatively to control tachyarrhythmias or angina. However, the loss of β-adrenergic-dependent vasodilation in a patient with unopposed catecholamine-induced vasoconstriction can lead to dangerous increases in blood pressure. Therefore, β-adrenergic blockers should not be used without prior α-adrenergic blockade to counteract vasoconstriction. β-adrenergic blockers used in preoperative preparation include propranolol, atenolol, metoprolol, and labetalol. Labetalol is a β-adrenergic blocker with some α-blocking properties and has the side effect of paradoxically increasing blood pressure. Reduced blood volume associated with chronic vasoconstriction may be observed in patients with PHEO. Therefore, preoperative volume expansion through saline infusion or increased water intake is recommended to reduce postoperative hypotension. [1,5,7,9,10,21]

Surgery

The overall perioperative mortality ranges around 2.4%; however, isolated reports describe cases even reaching 24%. Among surgical complications, splenectomy is often mentioned, with its frequency being higher in open exploration of the abdominal cavity than in laparoscopic procedures. The risk of surgical complications appears to be higher in patients with severe hypertension and those requiring reoperation. Effective reduction of the risk of death and surgical complications can be achieved through appropriate preoperative patient preparation, precise tumor localization, and careful intraoperative care. [1,5,7,9,10]

Laparoscopy

The majority of pheochromocytomas can be removed through laparoscopic surgical procedures, which have become the preferred method for adrenal tumors with a diameter not exceeding 6 cm. Laparoscopic adrenal surgery typically involves making four small incisions, each about 10-12 mm in diameter, in the subcostal area. Currently, laparoscopic surgery is widely used because it allows for tumor localization before the operation. However, tumors with greater invasiveness or a diameter exceeding 6 cm may be more difficult to remove laparoscopically and may require open surgical procedures. For larger pheochromocytomas, a lateral laparoscopic approach can be used, providing better exploration of the abdominal cavity and assessment of the liver for metastases. For patients with small adrenal pheochromocytomas, as well as those who have undergone previous abdominal surgeries, a posteriorly accessed laparoscopic approach may be preferred. Laparoscopy enables detailed

magnified images of the pheochromocytoma and its vasculature. To reduce the risk of cell fragmentation and dissemination, pheochromocytomas are carefully surrounded during laparoscopic procedures. Larger tumors can be removed through an extended laparoscopic incision, allowing for surgeon-assisted adrenalectomy. The use of laparoscopic techniques reduces the frequency and severity of hypotensive episodes and postoperative pain, shortens recovery time and hospitalization. It is the least invasive surgical method, enabling patients to quickly mobilize and return to daily activities. Laparoscopic surgery can be performed on pregnant women and may also be effective for some extra-adrenal tumors. In specialized centers, the operative mortality rate is below 3%. [1,5,7,9,10,11]

Mini-laparoscopic surgery

This procedure requires the creation of three small incisions, approximately 2-5 mm in diameter, in the subcostal area, and one larger incision in the umbilicus for tumor removal. A study conducted on 15 patients found that this technique reduces the duration of surgery and the recovery period compared to traditional adrenalectomy methods. However, prior significant experience in performing laparoscopic procedures is necessary. [1,5,7,9,10,14]

Cortex-sparing surgery

All patients who undergo bilateral adrenalectomy must take glucocorticoids and mineralocorticoids substitutionally for their entire lives. In order to avoid adrenal insufficiency in patients with benign or bilateral adrenal tumors, selective laparoscopic resection of small tumors with preservation of the adrenal cortex is often performed. Unfortunately, this cortex-sparing technique is associated with a higher risk of recurrence, reaching approximately 24%. [1,5,7,9,10,14]

Open laparotomy

Patients with large chromaffin tumors or pheochromocytomas, especially when there is a need to reduce the mass of metastases in the abdominal cavity, often require open laparotomy. Incisions in the midline anterior or subcostal region are commonly used to obtain adequate surgical access. For patients with bladder pheochromocytomas, partial cystectomy may sometimes be necessary. However, in the case of larger pheochromocytomas, total cystectomy may be necessary, followed by the creation of a bypass ureteroenterostomy if the

tumor is not completely removed. After total cystectomy, there is also the possibility of creating a new bladder from segments of the small intestine. [1,5,7,9,10,14]

In case of paroxysmal hypertension, intravenous phentolamine is administered at a dose of 2-5mg, and injections can be repeated as needed. [5]

If primary tumor removal is not possible or non-operative metastases occur, doxazosin is used at a dose of 1-8mg per day, divided into 2 doses. [5]

Postoperative Monitoring Guidelines:

1. Immediate Postoperative Period (First Month):

- Laboratory tests should be conducted to assess immediate postoperative outcomes.

2. 6-Month Follow-Up:

- Repeat laboratory tests at the 6-month mark to monitor recovery and identify any potential issues.

3. 1-Year Follow-Up:

- Another round of laboratory tests should be conducted at the 1-year mark to evaluate long-term recovery and assess any lingering effects.

- Imaging studies should also be performed at this time to ensure there are no structural abnormalities or complications.

4. Subsequent Annual Follow-Ups:

- If results remain within normal range, annual laboratory tests should be conducted to monitor the patient's ongoing health status and detect any signs of recurrence or complications.

[1,5,7,9,10,21]

Radiotherapy and Chemotherapy

The treatment of inoperable malignant tumors is a well-documented therapeutic area, and one of the methods used in clinical practice is therapy using 131I-MIBG. Additionally, the combination of cyclophosphamide, vincristine, and dacarbazine has been effectively used in chemotherapy regimens. There is also experimentation with the use of somatostatin receptor agonists, such as octreotide.

For inoperable malignant pheochromocytomas and pituitary adenocarcinomas, isotope therapy using 131I-MIBG serves as an alternative, often with a palliative intent. Typically, 4-6 cycles of treatment are administered, with doses ranging from 150 to 200 mCi, spaced at three-month intervals. Recently, there has been consideration of the potential use of somatostatin analogs labeled with radioactive isotopes, such as yttrium (Y) or lutetium (Lu), although there is still a lack of sufficient data confirming the effectiveness of this therapy. [1,5]

Prognosis

Over 95% of patients with a benign form of PPGL survive five years after diagnosis. However, for the malignant form, the five-year survival rate is below 50%. In pregnant women, the presence of PPGL carries a high risk of mortality for both the mother and the fetus. Although available epidemiological data are limited, they suggest a possible increased risk of other tumors in individuals affected by PPGL in the long term. [1,5,7,9,10]

Discussion

The clinical presentation of pheochromocytoma (PHEO) can be so complex that it has earned the nickname "the great mimicker." Although the classic triad of PHEO symptoms includes palpitations, headaches, and excessive sweating, many other symptoms may also occur. When PHEO is suspected, checking serum metanephrine levels and increased 24-hour urinary fractionated metanephrine excretion is necessary. In cases of doubtful laboratory values, a clonidine suppression test is performed. The best imaging study is computed tomography (CT), although in cases where radiation exposure is to be avoided or metastases are suspected, magnetic resonance imaging (MRI) can be used. When the diagnosis or imaging results are inconclusive, consideration is given to performing (123I)-MIBG scanning. If the (123I)-MIBG scan result is negative and clinical suspicion persists, a PET scan with FDG is recommended. According to the American Society of Clinical Oncology (ASCO) recommendations, patients with over 10% probability of carrying a hereditary mutation predisposing to cancer should undergo genetic testing. Before surgery, the patient should receive an appropriate α1 blocker, usually phenoxybenzamine, for at least 10-14 days. Calcium channel blockers and/or β-blockers may be used as alternative or adjunctive treatments. Postoperative monitoring includes regular laboratory tests in the first month after surgery, again at 6 months, and then annually, along with imaging studies after one year. If laboratory test results remain stable, lifelong monitoring of the patient is necessary. [1,5,7,9,10,21]

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References

[1] Endokrynologia ogólna i kliniczna Greenspana. Tom 1. David G. Gardner, Dolores Shoback, 2013r, s 456-490.

[2] Interna Szczeklika 2022. Piotr Gajewski. 2022r, s 1492-1495.

[3] Borgis - Postępy Nauk Medycznych 8/2008, s. 491-495

[4] Borgis - Postępy Nauk Medycznych 8/2008, s. 510-514

[5] Wielka interna – Endokrynologia tom II. Wojciech Zgliczyński, 2020r, s 74-80

[6] Orpha.net - Orpha number: ORPHA116 „Beckwith-Wiedemann syndrome"

[7] Farrugia, Frederick-Anthony, and Anestis Charalampopoulos. "Pheochromocytoma." Endocrine regulations vol. 53,3 (2019): 191-212. doi:10.2478/enr-2019-0020

[8] Carrasquillo, Jorge A et al. "Imaging of Pheochromocytoma and Paraganglioma." Journal of nuclear medicine : official publication, Society of Nuclear Medicine vol. 62,8 (2021): 1033-1042. doi:10.2967/jnumed.120.259689

[9] Farrugia, F A et al. "Pheochromocytoma, diagnosis and treatment: Review of the literature." Endocrine regulations vol. 51,3 (2017): 168-181. doi:10.1515/enr-2017-0018

[10] Lima, José Viana Júnior, and Claudio Elias Kater. "The Pheochromocytoma/Paraganglioma syndrome: an overview on mechanisms, diagnosis and management." International braz j urol : official journal of the Brazilian Society of Urology vol. 49,3 (2023): 307-319. doi:10.1590/S1677-5538.IBJU.2023.0038

[11] Clifton-Bligh, Roderick J. "The diagnosis and management of pheochromocytoma and paraganglioma during pregnancy." Reviews in endocrine & metabolic disorders vol. 24,1 (2023): 49-56. doi:10.1007/s11154-022-09773-2

[12] Eisenhofer, Graeme et al. "Pheochromocytoma." Clinical chemistry vol. 59,3 (2013): 466-72. doi:10.1373/clinchem.2012.182246

[13] Eisenhofer, Graeme. “Pheochromocytoma: recent advances and speed bumps in the road to further progress.” Journal of hypertension vol. 24,12 (2006): 2341-3. doi:10.1097/HJH.0b013e328010b9bf

[14] Yip, Linwah et al. “Surgical management of hereditary pheochromocytoma.” Journal of the American College of Surgeons vol. 198,4 (2004): 525-34; discussion 534-5. doi:10.1016/j.jamcollsurg.2003.12.001

[15] Asari, Reza et al. “Estimated risk of pheochromocytoma recurrence after adrenal-sparing surgery in patients with multiple endocrine neoplasia type 2A.” Archives of surgery (Chicago, Ill. : 1960) vol. 141,12 (2006): 1199-205; discussion 1205. doi:10.1001/archsurg.141.12.1199

[16] Walther, M M et al. “Management of hereditary pheochromocytoma in von Hippel-Lindau kindreds with partial adrenalectomy.” The Journal of urology vol. 161,2 (1999): 395-8.

[17] Petri, B-J et al. “Phaeochromocytomas and sympathetic paragangliomas.” The British journal of surgery vol. 96,12 (2009): 1381-92. doi:10.1002/bjs.6821

[18] Benn, Diana E, and Bruce G Robinson. “Genetic basis of phaeochromocytoma and paraganglioma.” Best practice & research. Clinical endocrinology & metabolism vol. 20,3 (2006): 435-50. doi:10.1016/j.beem.2006.07.005

[19] Derrou, Sara et al. “Pheochromocytoma and glucoregulation disorders.” Annals of African medicine vol. 20,1 (2021): 42-45. doi:10.4103/aam.aam_13_20

[20] Baez, Juan C et al. “Pheochromocytoma and paraganglioma: imaging characteristics.” Cancer imaging : the official publication of the International Cancer Imaging Society vol. 12,1 153-62. 7 May. 2012, doi:10.1102/1470-7330.2012.0016

[21] Renard, J et al. “Pheochromocytoma and abdominal paraganglioma.” Journal of visceral surgery vol. 148,6 (2011): e409-16. doi:10.1016/j.jviscsurg.2011.07.003