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Pheochromocytoma and Paraganglioma: Clinical Manifestations, Diagnostic Approaches, and Therapeutic Strategies

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Abstract: Pheochromocytomas and paragangliomas are rare neuroendocrine tumors derived from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia. These tumors are characterized by excessive or episodic secretion of catecholamines, leading to variable clinical presentations ranging from asymptomatic adrenal masses to severe hypertensive crises. Although uncommon, they are clinically significant because they represent a potentially curable cause of secondary hypertension. Genetic predisposition plays a major role, with up to 25% of cases associated with hereditary syndromes such as multiple endocrine neoplasia type 2 (MEN2), von Hippel–Lindau (VHL) disease, and neurofibromatosis type 1 (NF1). Advances in biochemical testing and imaging have improved diagnostic accuracy, while surgical excision remains the mainstay of therapy. Early recognition, careful preoperative management, and long-term follow-up are critical to reducing morbidity and mortality.

Keywords: pheochromocytoma, paraganglioma, catecholamines, secondary hypertension, chromaffin cells, adrenal tumor

Introduction

Pheochromocytoma is a catecholamine-producing tumor of the adrenal medulla, whereas paragangliomas arise from extra-adrenal sympathetic or parasympathetic paraganglia. Although these tumors are rare, their clinical importance is disproportionate due to the risk of life-threatening cardiovascular complications. The “classic triad” of episodic headache, sweating, and palpitations, combined with paroxysmal hypertension, remains a hallmark of the disease. However, clinical presentation may vary widely, posing diagnostic challenges. Improved understanding of genetic contributions and tumor biology has reshaped the approach to diagnosis and management, emphasizing the need for timely detection and comprehensive evaluation.

Epidemiology

The estimated incidence of pheochromocytoma is 2–8 cases per million population per year. Approximately 0.1% of patients with hypertension harbor pheochromocytoma, making it an important cause of secondary hypertension. Autopsy studies suggest a prevalence of around 0.2%. The mean age at diagnosis is 40 years, though tumors may occur at any age, including childhood. The classic “rule of tens” states that 10% of tumors are bilateral, 10% are extra-adrenal, and 10% are malignant. However, with better genetic insights, these proportions are known to be higher in hereditary syndromes. In Uzbekistan, there is however limited data specifically quantifying the incidence of pheochromocytoma independent of other adrenal tumors. Retrospective analysis at the Republican Scientific and Practical Medical Center of Endocrinology (2021-2024) involving 89 patients with adrenal origin hypertension found that 21 patients (≈23.6%) had pheochromocytoma. Among a larger cohort of 282 individuals presenting with various adrenal tumors, pheochromocytoma comprised approximately 18.1% (51 cases). The age range of these patients was from 4 months to 74 years (mean age ~39.8 ± 15.7 years), with a higher proportion of females (~59.9%). These figures suggest that pheochromocytoma is a significant subset of adrenal tumors presenting with hypertension in Uzbekistan, though population-based incidence rates remain to be established.

Etiology and Pathogenesis

Most pheochromocytomas arise sporadically, but about 25% are associated with inherited syndromes. Germline mutations in genes such as **RET, VHL, NF1, SDHB, SDHC, SDHD, and SDHAF2** are implicated. These mutations alter cellular metabolism, mitochondrial function, or cell cycle regulation. For example:

- **VHL mutations** impair degradation of hypoxia-inducible factors, promoting angiogenesis and tumorigenesis.
- **RET mutations** activate tyrosine kinase signaling, driving cell proliferation.
- **SDH mutations** disrupt the Krebs cycle and electron transport chain, leading to increased oxidative stress and tumor formation.

Pathologically, these tumors are highly vascularized, with chromaffin cells staining dark due to catecholamine oxidation. Excess catecholamine secretion causes episodic or sustained adrenergic crises, producing cardiovascular, neurological, and metabolic symptoms. Succinate dehydrogenase (SDH) is an enzyme of the Krebs cycle and the mitochondrial respiratory chain. The VHL protein is a component of a ubiquitin E3 ligase. VHL mutations reduce protein degradation, resulting in upregulation of components involved in cell cycle progression, glucose metabolism, and oxygen sensing. In addition to germline mutations, somatic mutations have been observed in >20 genes, broadly grouped into three different clusters of pathogenetically relevant genes: cluster 1, the pseudohypoxia group comprising mainly the genes SDHx (subunits of SDH), FH, VHL, and HIF2A; cluster 2, the kinase signaling group (RET, NF1, TMEM127, MAX, HRAS, KIF1Bβ, PDH); and cluster 3, the Wnt signaling group (CSDE1, MAML3).

Clinical Features

The clinical spectrum is highly variable, depending on the degree and pattern of catecholamine secretion.

1. **Cardiovascular:**
   - Persistent or paroxysmal hypertension
   - Tachycardia, palpitations
   - Orthostatic hypotension
   - Arrhythmias, chest pain, or heart failure
2. **Neurological:**
   - Severe episodic headaches
   - Anxiety, panic attacks
   - Tremors, sweating
   - Visual disturbances
3. **Gastrointestinal:**
   - Nausea, vomiting
   - Abdominal pain, constipation
4. **Metabolic:**
   - Weight loss, hyperglycemia
   - Heat intolerance
5. **Paroxysms (Adrenergic crises):**

Episodes lasting 15–60 minutes characterized by severe headache, sweating, palpitations, tremors, flushing, and a sense of impending doom. Triggers may include physical activity, stress, certain drugs, or tyramine-containing foods.

The dominant sign is hypertension. Classically, patients have episodic hypertension, but sustained hypertension is also common. Catecholamine crises can lead to heart failure, pulmonary edema, arrhythmias, and intracranial hemorrhage. During episodes of hor mone release, which can occur at widely divergent intervals, patients are anxious and pale, and they experience tachycardia and palpita tions. These paroxysms generally last

Diagnosis

The diagnosis is based on documentation of catecholamine excess by biochemical testing and localization of the tumor by imaging. These two criteria are of equal importance, although measurement of cat echolamines or metanephrines (their methylated metabolites) is tradi tionally the first step in diagnosis.

1. **Biochemical Testing:**

- Plasma free metanephrines (most sensitive)
- 24-hour urinary fractionated metanephrines and catecholamines
- Plasma catecholamines (less sensitive but supportive)

2. **Imaging Studies:**

- CT or MRI to localize adrenal or extra-adrenal tumors
- MIBG scintigraphy for functional imaging, especially in metastatic or extra-adrenal cases
- PET scanning in difficult-to-localize tumors

3. **Genetic Testing:**

Recommended for young patients, bilateral tumors, or positive family history, to identify hereditary syndromes and guide screening.

Differential diagnosis

When the possibility of a pheochromocy toma is being entertained, other disorders to consider include essential hypertension, anxiety attacks, use of cocaine or amphetamines, mastocy tosis or carcinoid syndrome (usually without hypertension), intracranial lesions, clonidine withdrawal, autonomic epilepsy, and factitious crises (usually from use of sympathomimetic amines). When an asymptomatic adrenal mass is identified, likely diagnoses other than pheochromocy toma include a nonfunctioning adrenal adenoma, an aldosteronoma, and a cortisol-producing adenoma (Cushing's syndrome).

Management

1. Preoperative Preparation

Preoperative optimization is crucial to reduce perioperative morbidity and mortality, particularly the risk of hypertensive crises during anesthesia induction and tumor manipulation.

- Alpha-adrenergic blockade:
- ✓ First-line therapy (e.g., phenoxybenzamine – non-selective, irreversible α-blocker; or doxazosin – selective α1-blocker).
- ✓ Initiated 7–14 days before surgery to achieve blood pressure control and normalize plasma volume.
- Beta-adrenergic blockade:
- ✓ Added only after adequate alpha-blockade if reflex tachycardia or arrhythmias develop.

- ✓ Propranolol or atenolol may be used. Beta-blockers must never be started before alpha-blockade, as this can precipitate a hypertensive crisis.
- ➢ Volume expansion:
- ✓ High-salt diet and liberal fluid intake are recommended to restore intravascular volume, which is chronically contracted due to catecholamine excess.
- ✓ Prevents severe postoperative hypotension.
- ➢ Surgical Treatment
- ✓ Laparoscopic adrenalectomy: Preferred for small to medium-sized benign adrenal tumors.
- ✓ Open adrenalectomy: Indicated for large tumors (>6 cm), suspected malignancy, or local invasion.
- ✓ In hereditary syndromes (e.g., MEN2, VHL), cortical-sparing adrenalectomy may be considered to preserve adrenal function and avoid lifelong steroid replacement.

2. Postoperative Management

- ➢ Hemodynamic monitoring: Risk of hypotension due to sudden catecholamine withdrawal and prior alpha-blockade.
- ➢ Hypoglycemia surveillance: Catecholamines antagonize insulin; sudden removal of excess catecholamines may lead to rebound hypoglycemia post-surgery.
- ➢ Hormonal follow-up: Plasma or urinary metanephrines should be rechecked to confirm biochemical cure.

3. Management of Malignant or Unresectable Disease

- ➢ Radiopharmaceutical therapy:
- ✓ MIBG (131I-metaiodobenzylguanidine) therapy in MIBG-avid tumors.
- ✓ 177Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) for somatostatin receptor–positive paragangliomas.

1. Systemic chemotherapy: Combination regimens such as cyclophosphamide, vincristine, and dacarbazine (CVD protocol) in aggressive disease.
2. Targeted therapies: Tyrosine kinase inhibitors (sunitinib, cabozantinib) may be considered in refractory cases.
3. Genetic testing and counseling: Recommended in all patients, as up to 40% of cases are associated with germline mutations (e.g., RET, VHL, SDHx).

Prognosis and Follow-up

Most pheochromocytomas are benign, and surgical resection is curative. However, recurrence can occur, especially in hereditary cases. Lifelong follow-up with periodic biochemical testing and imaging is recommended. Malignant pheochromocytomas, although rare, have poor prognosis and require multidisciplinary care.

Conclusion

Pheochromocytomas and paragangliomas, though rare, represent critical causes of secondary hypertension with significant morbidity and mortality. Their diverse clinical presentation, genetic heterogeneity, and potential for life-threatening complications necessitate a comprehensive diagnostic and therapeutic approach. Advances in biochemical assays, imaging, and genetic testing have transformed early recognition and risk stratification. Surgical resection remains the definitive treatment, but outcomes depend on meticulous preoperative management and lifelong surveillance. Improved understanding of molecular pathways holds promise for novel therapies, offering hope for patients with malignant or recurrent disease.

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