Pheochromocytoma and Paraganglioma

Genetics, Diagnosis, and Treatment

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KEYWORDS

• Pheochromocytoma • Paraganglioma • Genetics • Treatment • Malignant
• Metastatic

KEY POINTS

- Pheochromocytomas and paragangliomas (PCCs/PGLs), both benign and malignant, have high morbidity and mortality, especially when not properly diagnosed or treated.
- Blood pressure management, usually with the alpha-blocker phenoxybenzamine, is critical perioperatively for all patients and surrounding treatments for those with metastatic disease.
- Surgery is the only cure for PCC/PGL, but limited biochemical and tumor control of metastatic disease occurs with treatments, including ^{131}I-MIBG, chemotherapy, and radiation.
- Up to 40% of patients with PCC/PGL have germline mutations in susceptibility genes; therefore, all patients should be considered for clinical genetic testing.
- Future work is needed to identify predictors of metastatic potential and novel targets for therapy.

INTRODUCTION

Neuroendocrine tumors arising from the adrenal medulla and extra-adrenal ganglia are called pheochromocytomas and paragangliomas (PCCs/PGLs), respectively. PCCs/PGLs are rare tumors with an incidence of 2 to 8 per million.[1] PCCs/PGLs occur in 0.2% to 0.6% of hypertensive patients and account for up to 5% of adrenal incidentalomas.[2] Most PCCs/PGLs are benign yet associated with high morbidity and mortality secondary to hypersecretion of catecholamines and metanephrines leading to hypertension, cardiovascular disease and even death. Approximately a quarter of PCCs/PGLs are malignant, defined by the World Health Organization as the presence

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of distant metastases.[1] Diagnosing PCCs/PGLs can be challenging, and treatments for metastatic disease are most often not curative. This review discusses the inherited genetics, diagnosis, and treatment of PCCs/PGLs.

GENETICS

Up to 40% of patients with PCCs/PGLs have a germline mutation in a known susceptibility gene,[3–5] more than any other solid tumor type. **Table 1** describes the susceptibility genes and the associated syndromes. The risk of PCC/PGL with each syndrome is discussed in the following sections.

Classic Tumor Syndromes

Neurofibromatosis type 1 (NF1) is an autosomal dominant syndrome found in 1 in 3000 individuals caused by mutations in the *NF1* gene. The diagnosis of NF1 is made when patients meet at least 2 of the clinical criteria (see **Table 1**).[6] PCCs, although not in the diagnostic criteria, occur at a higher frequency than in the general population. Approximately 5% of patients develop unilateral or bilateral PCC, and 12% of those are metastatic.[6] The mean age at diagnosis of PCC is 42, similar to sporadic PCC. Guidelines suggest screening for PCC in patients with NF1 who have hypertension.[6]

Multiple endocrine neoplasia type 2 (MEN2) is an autosomal dominant syndrome found in 1 in 30,000 individuals caused by activating mutations in the *RET* proto-oncogene. There are 3 subgroups of MEN2 described in **Table 1**. MEN2A accounts for more than 90% of cases, whereas MEN2B and the rare familial medullary thyroid cancer subtype account for the rest.[7] Fifty percent of patients with MEN2 develop PCC and half have bilateral disease. There are strong genotype phenotype correlations; therefore, screening recommendations for PCC vary depending on the mutation.[7] Patients with MEN2A with *RET* codon 630 or 634 mutations and patients with MEN2B (most with *RET* codon 918 mutations) should begin screening for PCC at age 8. Patients with all other MEN2A mutations should begin screening for PCC at age 20. The mean age at diagnosis of PCC is between 30 and 40 years old, and the malignancy rate is less than 5%.[7]

von Hippel Lindau disease (vHL) is an autosomal dominant syndrome affecting 1 in 36,000 births per year and caused by mutations in the *VHL* gene. vHL is defined by several benign and malignant tumors described in **Table 1**.[8] Unilateral or bilateral PCC occurs in 10% to 20% of patients, with rare reports of extra-adrenal or head and neck PGL (HNPGL).[8] Similar to MEN2, there are strong genotype phenotype correlations.[9,10] Patients with truncating mutations or exonic deletions in the VHL protein have a lower penetrance for PCC but a high penetrance for renal cell carcinoma. On the other hand, patients with missense mutations in VHL more frequently develop PCC when mutations are on the surface of the protein rather than the core.[11] Screening for PCC in patients with vHL should begin at age 5 for families with high-risk mutations. The mean age at diagnosis of PCC is 30 years old, and approximately 5% develop metastatic disease.[8]

Hereditary Paraganglioma Syndromes

Autosomal dominant mutations in succinate dehydrogenase (SDH), complex II of the mitochondrial respiratory chain, cause the hereditary paraganglioma syndromes. Mutations can occur in any of the subunit genes (*SDHA, SDHB, SDHC, SDHD*) or cofactor (*SDHAF2* also called *SDH5*) (see **Table 1**). SDHB is the most commonly mutated subunit leading to PCC/PGL. Mutation carriers develop extra-adrenal PGL