Pheochromocytoma and Paraganglioma

Diagnosis, Genetics, and Treatment

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KEYWORDS

• Neuroendocrine tumor • Pheochromocytoma • Paraganglioma
• Biochemical evaluation • Genetics • Imaging • Perioperative management • Surgery

KEY POINTS

- Pheochromocytomas and paragangliomas (Pheo/PGL) are rare neuroendocrine tumors that are being discovered incidentally at an increasing rate.
- At least one-quarter of patients with Pheo/PGL display germline mutations; genetic testing plays an increasingly important role in the evaluation and management of these patients.
- Plasma-free metanephrines and urinary fractionated metanephrine levels are highly sensitive in the diagnosis of Pheo/PGL.
- Selective or nonselective alpha blocking agents and calcium channel blockers appear to be equally effective in treating the physiologic effects of Pheo/PGL.
- Several surgical approaches are used to remove Pheo/PGL, and the choice of approach depends on patient and tumor-related factors, as well as surgeon preference.

INTRODUCTION: NATURE OF THE PROBLEM

The terms paraganglioma (PGL) and pheochromocytoma (Pheo) were first mentioned in 1908 and 1912 respectively when pathologists Henri Alezais, Felix Peyron, and Ludwig Pick noted tumors with a positive chromaffin reaction in extra-adrenal and adrenal chromaffin tissue. However, according to Welborne and colleagues[1] it was not until 1922, when Marcel Labbe and colleagues[2] reported a case of symptomatic paroxysmal hypertension in a patient with a Pheo, that the relationship between the tumor and its symptoms was established.

The first successful resection for Pheo was performed by Cesar Roux in February 1926. The patient, Madam S, was 33 years old and had suffered attacks of vertigo

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and nausea for 2 years. At laparotomy, she was found to have a 13-cm adrenal Pheo. Charles Mayo performed the second and perhaps better-known resection for Pheo in October 1926. The patient, Mother Joachim, a nun from Canada, suffered from paroxysmal hypertension, weakness, vomiting, and headaches. At the time, it was felt that her hypertension was mediated through the sympathetic nerves and that sympathectomy may provide relief. She underwent an exploratory laparotomy, and a tumor "the size of a lemon" was found behind the tail of her pancreas. Without preoperative pharmacologic blockade, the entire procedure was completed in 64 minutes and the patient recovered well.[1,3]

By 1934, more than 60 patients had been diagnosed with a Pheo or PGL and by 1940, 20 successful operations had been performed. The operative mortality in these early series was 30% to 45%.[4] These high mortality rates were partly due to a lack of preoperative alpha blockade and modern anesthesia management. Since that time, much has been learned about the management of these rare tumors. Herein we discuss the incidence and prevalence of Pheo/PGL; describe the typical clinical presentation and diagnostic evaluation of these tumors; explore the known genetic associations; and summarize the preoperative, intraoperative, and postoperative management strategies.

EPIDEMIOLOGY

The annual incidence of Pheo and PGL is between 2 and 8 per million and the prevalence in the population is 1:6500 to 1:2500, respectively.[5] Pheo/PGLs are thought to occur in 0.05% to 0.1% of patients with sustained hypertension. However, this accounts for only 50% of people with Pheo/PGL because approximately half of patients will have paroxysmal hypertension or normotension.[5] Pheochromocytomas comprise 4% to 8% of all adrenal incidentalomas.[6–9] The peak age of occurrence is in the third to fifth decade of life. Today, 10% to 49% of Pheo/PGLs are found incidentally during imaging studies obtained for other reasons.[10–14]

In 1951, John Graham[15] analyzed the records of 207 Pheo/PGLs and concluded that Pheo/PGLs follow the "rule of 10s," with 10% occurring in extra-adrenal tissues, 10% bilateral, and 10% malignant. Later, the teaching that 10% of these tumors were familial was added to this rule. Although this teaching persists in many textbooks and medical school lectures, studies have shown that the "rule of 10" no longer applies. Approximately 15% to 25% of Pheo/PGLs originate in extra-adrenal chromaffin tissue,[16,17] 8% of sporadic and 20% to 75% of hereditary Pheo/PGL are bilateral at presentation,[18–20] 5% of adrenal-based and 33% extra-adrenal tumors are malignant,[14] and at least 24% of sporadic Pheo/PGLs have a genetic basis.[18] Today, bilaterality, extra-adrenal location, and prevalence of malignancy depend directly on the underlying genetic mutation.

PATHOPHYSIOLOGY

Pheo/PGLs are neuroendocrine tumors that arise from paraganglia cells derived from the neural crest and are distributed along the paravertebral and para-aortic axis from the base of the skull to the pelvic floor. Adrenal-based Pheos arise in the sympathetic adrenal chromaffin cells. Extra-adrenal sympathetic PGLs most commonly occur around the inferior mesenteric artery or at the aortic bifurcation in the organ of Zuckerkandl, but can occur in any chromaffin tissue in the thorax, abdomen, and pelvis. Almost all adrenal-based Pheos and extra-adrenal sympathetic PGLs produce, store, metabolize, and secrete catecholamines or their metabolites.[5] Extra-adrenal parasympathetic PGLs are most commonly found in the head and neck region and are