

PHEOCHROMOCYTOMA

THE FACTS YOU NEED TO KNOW



What is a Pheochromocytoma?

Pheochromocytomas (PCCs) are tumors of the chromaffin cells that arise within the adrenal medulla. They belong to a group of diseases termed neuroendocrine tumors (NETs). Pheochromocytomas are related to another group of endocrine tumors called paragangliomas which occur outside the adrenal gland and originate at any level of extra-adrenal paraganglia (from the skull base to the pelvic floor). Although pheochromocytomas and paragangliomas share many tumor characteristics on a cellular level, differentiation between them by the physician and accurate diagnosis are necessary to establish the correct management plan and appropriate genetic testing and prognosis.

Pheochromocytomas-paragangliomas (PPGL) are biochemically-active endocrine tumors that often produce hormones called catecholamines (epinephrine and norepinephrine), causing serious health implications if left untreated. In addition, these tumors can originate in multiple locations of the body, where they can metastasize and become a form of cancer.

The diagnosis of pheochromocytoma is often delayed, impacting patients and their families. In part, these tumors can have an insidious course with non-specific symptoms, and in many cases they can be silent tumors. The patient presentations vary widely and, while some patients have many of the associated symptoms, others have no symptoms at all due to the silent nature of their tumors. Therefore, the diagnosis and management of these uncommon tumors should be carried out in specialized centers with expertise in the management of these tumors.

What Causes Pheochromocytoma?

Pheochromocytomas are caused by germline mutations in about 40% of patients (these are mutations that can be inherited), or as part of other familial syndromes, but they also can be sporadic caused by somatic mutations (these mutations occur in the tumor cells only and cannot be inherited) or other genetic alterations at a cellular level.

Is Genetic Testing Necessary?

The field of pheochromocytoma-paraganglioma (PPGL) is rapidly evolving. Many discoveries over the last decade have significantly improved our understanding of the disease. The identification of new hereditary forms of PPGL has led to the highest rate of germline susceptibility in cancer genetics at almost 40%. Currently 22 susceptibility genes have been identified in which mutations can occur, causing the patient to develop these tumors. Many of these gene mutations can be inherited and passed to the patient's children.

The genetic cause can dictate the behavior of these tumors to some extent; experts in the field call this genotype-phenotype correlation. These include associated biochemical profile, tumor location, malignant potential, aggressive clinical behavior, and overall prognosis. Furthermore, genetic identification provides valuable information for establishing a treatment plan and procures the rationale for appropriate guidance for follow-up surveillance. Therefore, genetic testing is of profound importance for all patients and their offspring, but this testing should be initiated as part of a multidisciplinary team in a specialized center.

Can Children of Patients Develop the Disease?

In some cases of pheochromocytoma where germline mutations are the basis of the disease, many of these mutations can be passed on to the patient's offspring, making it necessary to test the children of the patients. If children are found to carry the mutation, they will need to follow up with an expert physician and undergo periodic active surveillance for early detection of the tumors.

Can Pheochromocytoma be a Part of Other Syndromes?

Pheochromocytoma can be a solitary disease affecting only the adrenal gland, and in other situations they can develop alongside paraganglioma in some genetic mutations, such as those of the following genes: SHDA, SDHB, SDHC, SDHD. In addition, they can appear as one manifestation in the setting of other syndromes, such as Multiple Endocrine Neoplasia type 2 (MEN2), von Hippel-Lindau (VHL), neurofibromatosis type 1 (NF1), Carney dyad, Carney triad, Pacak-Zhuang syndrome.

Can Other Tumors Develop with Pheochromocytoma?

In cases where pheochromocytoma is a manifestation of other syndromes, association with other tumors or cancers can occur. This varies by the type of associated familial syndrome. For example, patients with SDHB could develop paragangliomas, gastrointestinal stromal tumors (GIST), kidney tumors and pituitary tumors. Patients with von Hippel-Lindau can develop a type of kidney cancer and central nervous system tumors in addition to neuroendocrine tumors and PPGL. Patients with MEN2 can develop parathyroid tumors and medullary thyroid cancer in addition to their susceptibility for pheochromocytoma. Patients with Pacak-Zhuang syndrome develop rare tumors called somatostatinomas.

What are the Signs and Symptoms of Pheochromocytoma?

The clinical presentation varies widely from silent tumors to very aggressive tumors causing life-threatening symptoms; this variation is based on the hormonal activity status of these tumors and the type of hormone they are producing. The symptoms can be caused by the mass effect of the tumors, such as abdominal or flank pain, or by the excess catecholamine production. The most common symptoms seen are diaphoresis, palpitations, blood pressure fluctuations, and dizziness. Spikes in blood pressure can occur and can be life threatening if not treated appropriately. Some patients present with anxiety as the sole symptom, in which case diagnosis can be difficult to establish.

How is Pheochromocytoma Diagnosed?

- Internists and endocrinologists suspect pheochromocytoma when they see unexplained symptoms suggestive of the disease.
- Work up should be done in a controlled setting under very strict criteria and protocol.
- Plasma or urine tests establish elevation of catecholamines or metanephrines (metabolites of catecholamines).
- Imaging studies can be used to establish the location of the tumors. These include anatomical imaging with CT or MRI and Functional Imaging with DOTATATE and other PET scans.
- Once diagnosis is established, blood is analyzed for a genetic panel of genes known to cause pheochromocytoma or paraganglioma.

How is Pheochromocytoma Treated?

The first step any patient should take is establishing care at a specialized center with physicians who have treated at least a few hundred patients with these syndromes. Since the disease is considered "rare," a referral to a specialist who is well-acquainted with the recent advancements in the treatment, management, localization methods and ongoing active research is essential.

After comprehensive evaluation and confirming the diagnosis, this is followed by advanced imaging studies to localize and stage the disease to establish a treatment plan and the prognosis.

Medical therapy by expert endocrinologists is the initial step in management, and this starts with special medications that control blood pressure and heart rate and block the active hormones from causing damage on the body.

When lesions are confined to the adrenal gland, or resectable extra-adrenal lesions are found, surgery follows. This occurs after very careful monitoring and medication optimization by the endocrinologist.

A common mistake we often encounter is failure to follow up with Endocrinology after the surgery. Unfortunately, in some circumstances failing to do so can result in tumor metastasis developing over the course of the years due to the absence of active surveillance by specialized centers.

Is preparation required before the surgery?

All surgeries have inherent cardiac risk associated with the stress of surgery and anesthesia, but pheochromocytoma surgery has a greater cardiac risk. These tumors often are biochemically active and produce catecholamines, including epinephrine and norepinephrine, which place the heart at additional risk. Therefore, blocking these hormones with the appropriate medications with appropriate titration and dosing is essential for good care management. Hydration status is also of important emphasis as the patient can become dehydrated.

What if I have unresectable, metastatic pheochromocytoma?

There are many other options for therapy available for the treatment of metastatic pheochromocytoma. Some of these therapies include the administration of targeted radioactive isotopes that attach specifically to tumor cells such as ¹³¹I MIBG, peptide receptor radioligand therapy (PRRT) such as Lutathera, or systemic therapy with chemotherapeutic agents.

Reference:

Alrezk, Rami, et al. "Update of Pheochromocytoma Syndromes: Genetics, Biochemical Evaluation, and Imaging." *Frontiers in Endocrinology* 9 (2018): 515.

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