Adrenal Gland Tumor: Current Approaches and Future Directions of Pheochromocytoma

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Received date: January 15, 2017; Accepted date: March 02, 2017; Published date: March 15, 2017.

Citation for this Article: Yellu Narsimha Reddy, Adrenal Gland Tumor: Current Approaches and Future Directions of Pheochromocytoma, Journal of Endocrinology and Disorders, DOI: 10.31579/2640-1045/003
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Abstract
Pheochromocytomas was a neuroendocrine tumor that arise from sympathetic and parasympathetic paraganglia. Because of the excess secretion of hormones, these tumors often cause debilitating symptoms and a poor quality of life. While medical management plays a significant role in the treatment of pheochromocytoma patients, surgical excision remains the only cure. Improved medical management and surgical techniques and an increased understanding of hereditary disease have improved the outcome of pheochromocytoma patients with benign disease; however, the outcome of patients with malignant disease remains poor. In this review, we discuss the presentation, diagnosis, management, and future directions in the management of this disease.

Key Words
Pheochromocytoma, Paraganglioma, Management, Clinical Presentation, Diagnosis

Introduction
These tumors can occur anywhere that sympathetic nervous tissue is found. While most pheochromocytomas arise in the adrenal medulla, there are also extra-adrenal pheochromocytomas (paragangliomas) of the abdomen, pelvis, thorax, and neck. Although these tumors are similar in origin, the clinical manifestations, prognosis, and management differ. The incidence of pheochromocytoma is <0.5% in patients with hypertensive symptoms and can be as high as 4% in patients with adrenal incidentalomas. Referrals for pheochromocytoma have been reported to be increasing, likely as a result of improved detection.

Because of excess secretion of the hormones epinephrine, nor epinephrine, dopamine, and others, patients with pheochromocytoma often experience debilitating symptoms and have a poor quality of life. Treatment for benign and malignant disease is surgical resection, while chemotherapeutic options for malignant disease remain poor. Recent advances in diagnostic imaging, pharmacologic treatment, surgical technique, and molecular profiling have contributed to a better understanding of the natural history of this disease.

Clinical presentation
Pheochromocytomas are rare tumors usually characterized by secretion of catecholamines and associated signs and symptoms of catecholamine excess. This secretion can arise in a sudden burst leading to paroxysmal symptoms. The classical symptom triad consists of palpitations, headaches and sweating lasting from only minutes to hours and occurring periodically on different occasions. Other symptoms, especially in an acute attack, include pallor, nausea and panic attacks, which may last for several minutes and resolve completely.

Apart from the above classic presentation, pheochromocytoma can also present with nonspecific symptoms such as flushing, nausea, tiredness or weight loss.

Abdominal pain and constipation or chest pain mimicking myocardial infarction as in the case of inverted takotsubo cardiomyopathy can be caused by sudden catecholamine release. A subtle sign may be new onset of diabetes, particularly in the young non-obese patient. Due to the diverse clinical manifestations, pheochromocytoma is therefore often referred as one of the great mimics in medicine. The first step in management of pheochromocytoma is to think of this rare disease and to then make the diagnosis.

Hypertension and incidentaloma
Pheochromocytoma is a rare cause of hypertension, but important because it is a usually curable cause of high blood pressure. The prevalence of the tumor among 4429 patients investigated for possible secondary hypertension has been reported at 0.3%. This is still higher than revealed in large autopsy studies, where the prevalence ranged from 0.05 to 0.09% in 44,680 and 15,984 deceased individuals respectively. Thus, pheochromocytoma should be considered in patients with hypertension, but generally only when secondary causes of high blood pressure are being considered or when there are other symptoms or signs of catecholamine excess that can alert the physician to the tumor. Prevalence of pheochromocytoma is much higher, at 4.2 to 6.5%, in patients screened for the tumor due to an incidentally discovered adrenal mass. All patients with adrenal masses should therefore be screened for pheochromocytoma, irrespective of the presence of hypertension and symptoms of catecholamine excess.

Familial Pheochromocytoma
Prior to 2000, it was generally accepted that 10% of pheochromocytomas were associated with familial syndromes; however, it is now recognized that the frequency of germline mutations in apparently sporadic presentations is as high as 15%–24%. Familial pheochromocytomas are often multifocal or bilateral and generally present at an earlier age than sporadic pheochromocytoma.
Germline mutations in six genes have been associated with familial pheochromocytoma, namely, the von Hippel-Lindau gene (VHL), which causes von Hippel-Lindau disease; the RET gene, leading to multiple endocrine neoplasia type 2 (MEN-2); the neurofibromatosis type 1 gene (NFI); the SDHx genes, which cause familial pheochromocytoma and/or paraganglioma; and the SDHB gene, which is associated with familial pheochromocytoma and/or paraganglioma. SDHB mutations appear to be the most common, with an overall frequency of 1.7%–6.7% in patients presenting with pheochromocytoma. Patients with SDHB mutations predominately develop extra-adrenal pheochromocytoma and are at high risk for malignant disease. Head and neck paragangliomas predominate in SDHD mutation carriers; however, they are more likely than SDHB carriers to have multifocal disease and less likely to be malignant. Importantly, both tumor types (pheochromocytoma or head and neck paraganglioma) may develop in SDHB or SDHD mutation carriers, which must be considered with the long-term monitoring of disease in these patients.

Results
Diagnosis
Much has been written about the diagnostic evaluation of pheochromocytoma. Useful decision algorithms have been proposed for a suspected pheochromocytoma, adrenal incidentaloma, and patients with a history of malignancy. As a general rule, pheochromocytomas are first established by a sensitive biochemical diagnosis and then confirmed by specific imaging studies. For the adrenal incidentaloma already discovered by computed tomography (CT) or magnetic resonance imaging (MRI), a biochemical diagnosis should be established before more specific imaging studies are done.

Biochemical Evaluation
Historically, many institutions relied upon 24-hour measurements of total urinary catecholamines and metanephrines. In studies from the Mayo Clinic, urinary measurements of total catecholamines and metanephrines were found to have a sensitivity and specificity of 98% and 98%, respectively. If a urinary collection is done, it is advisable to measure twice to account for the episodic nature of pheochromocytoma. Although urinary dopamine has a specificity of 99%, it is a poor first choice because of a sensitivity of 63%. Elevations in either urinary norepinephrine or epinephrine were found to have a sensitivity of 100% and a specificity of 97%. Unfortunately, the 24-hour collection method can place an undue burden on the patient. Tricyclic antidepressants can cause a false-positive result with the measurement of urinary catecholamines.

Historical tests worth mentioning include the glucagon stimulation test, chromogranin A, and direct measurements of plasma catecholamines. The glucagon stimulation test is infrequently used because it does not reliably increase hormonal secretion. Although the overlap with carcinoid tumors and adrenal cortical carcinoma lowers its specificity, serum chromogranin A levels were found to be elevated in 86% of patients with pheochromocytoma. While not directly useful in diagnosis, chromogranin A levels are useful in the management of malignant pheochromocytoma as a marker of tumor burden and progression of disease. Ultimately, the combination of different biochemical investigations does not increase diagnostic accuracy, and measurement of plasma free metanephrines is the preferred test in patients with both hereditary and sporadic disease.

Imaging
Imaging tests should be employed for localization after a biochemical diagnosis is confirmed.

With the exception of the smaller tumors seen in hereditary disease, CT and MRI are sensitive enough to localize most pheochromocytomas. Ninety-five percent of extra-adrenal pheochromocytomas are found in the abdomen and pelvis. Both CT and MRI have a sensitivity of 98%–100% for adrenal pheochromocytomas, but MRI is more sensitive (94% versus 90%) for extra-adrenal pheochromocytomas. Unfortunately, these tests have a specificity of approximately 70% because of the high incidence of adrenal incidentalomas.

Treatment of Pheochromocytoma
Preoperative Management
Once the diagnosis of a pheochromocytoma is made, appropriate preoperative medical management is necessary to reduce the risk for perioperative complications. During surgical manipulation of the tumor, massive catecholamine release may occur, which can exceed the normal plasma concentration by >1,000 times. This can result in hypertensive crisis, cardiac arrhythmias, cerebral vascular accident, myocardial infarction or ischemia, pulmonary edema, and multiorgan failure. The introduction of pharmacological pretreatment in the 1950s reduced the perioperative mortality rate from as high as 45% to <2%.

The aim of pharmacological management is to abolish or reduce the potentially lethal swings in blood pressure that can occur during induction of an anesthetic and surgical manipulation of the tumor, and to prevent the severe hypotension that can result immediately following removal of the tumor. Stabilization of blood pressure is achieved by the use of a single antihypertensive agent or a combination of antihypertensive agents preoperatively and intraoperatively to counteract excessive catecholamine adrenergic activity, volume expansion with i.v. fluid to prevent hypovolemia, and maximum vasodilatation is achieved, and inotropic support after excision of the pheochromocytoma if required. There are currently no randomized prospective trials to establish the optimal preoperative pharmacological management of pheochromocytoma.

Postoperative Management
Patients may require monitoring in a high-dependency unit or intensive care setting for the first 12–48 hours because cardiovascular and metabolic instability can occur. Blood pressure and volume should be monitored using invasive arterial pressure and central venous pressure monitoring. Postoperative hypotension can result from the persisting action of antihypertensive agents used in the pre- and postoperative phases of management, as well as adrenoreceptor downregulation resulting from chronic high levels of circulating catecholamines. Norepinephrine may be required to maintain blood pressure in the early postoperative period. Hypoglycemia can occur postoperatively and should be monitored for and corrected.

Future Directions
Much attention has recently been devoted to pheochromocytoma as the understanding of this disease continues to improve. Serum tests have achieved a high sensitivity and specificity, and new imaging techniques continue to develop. [123I]MIBG is superior to [131I]MIBG scintigraphy for the evaluation of metastases, but the availability of this scanning modality is not yet widespread in the U.S. While expensive, 6-18F-fluorodopamine PET is a selective and sensitive system that reliably locates both primary tumors and metastases. If it becomes widely available, it would greatly aid in the staging and management of malignant disease. Continually improving detection methods, especially screening of high-risk populations, will only contribute to the treatment and knowledge of these conditions in the future.

While treatment for benign pheochromocytoma remains surgical resection, therapy for malignant disease is unsatisfying at best. Combination therapy with [131I]MIBG and chemotherapy using cyclophosphamide, dacarbazine, and vincristine produced additive effects, but there was not a significant long-lasting benefit. Radiofrequency ablation of hepatic and bony metastases has shown symptomatic relief in some patients. Current studies focus on targeted pharmacologic interventions of specific pathways within pheochromocytoma cells, specifically Raf-1, glycerol synthase kinase-3β, and Notch-1.
These pathways are currently being targeted in clinical trials for carcinoids and medullary thyroid cancer, and future experiments will be directed toward clinical applications of these treatments. With a better understanding of the molecular mechanisms of these tumors, better treatments could become possible. The future is wide open for improvements in the understanding and treatment of this disease.

Conclusion

Although PHEO/PGL are very rarely diagnosed during childhood, it is imperative for the pediatric clinician to be able to recognize and screen for such tumors, particularly in the context of known familial disease. Advances in medicine have expanded our knowledge regarding the etiology, diagnosis, treatment, and long-term follow-up of these tumors. Optimal care of these children includes a multidisciplinary approach by endocrinologists, surgeons, genetic counselors, and radiologists/nuclear medicine experts who are experienced in the evaluation and treatment of these uncommon yet fascinating endocrine neoplasms.

References