

## Adrenal Gland Tumor: Current Approaches and Future Directions of Pheochromocytoma

<sup>1</sup>Yellu Narsimha Reddy, <sup>1</sup>Navya K

Department of Pharmacy Kakatiya University, Warangal, India

\*Corresponding Author : Yellu Narsimha Reddy, Department of Pharmacy Kakatiya University, Warangal, India.

E-mail: [ynrku@yahoo.co.in](mailto:ynrku@yahoo.co.in)

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: [10.31579/2640-1045/097](https://doi.org/10.31579/2640-1045/097)

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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 manifestation, 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 (VHL) syndrome, the *RET* gene, leading to multiple endocrine neoplasia type 2 (MEN-2), the neurofibromatosis type 1 gene (*NFI*), associated with neurofibromatosis type 1 (NF1) disease, and the genes encoding subunits B and D (and also rarely C) of mitochondrial succinate dehydrogenase (*SDHB*, *SDHD*, and *SDHC*), which are associated with familial paraganglioma/pheochromocytoma.

## Familial Pheochromocytoma/Paraganglioma Syndromes

Recently described germline mutations in *SDHB*, *SDHD*, and *SDHC* (previously *PGL4*, *PGL1*, and *PGL3*) result in 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 hypotension once maximal 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 adrenoceptor 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. <sup>123</sup>I-MIBG is superior to <sup>131</sup>I-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-<sup>18</sup>F-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 <sup>131</sup>I-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, glycogen synthase kinase-3 $\beta$ , 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

- Amar L., Bertherat J., Baudin E., Ajzenberg C., Bressac-De Paillerets B., Chabre O., et al. (2005b) Genetic Testing in Pheochromocytoma or Functional Paraganglioma. *J Clin Oncol* 23: 8812–8818.
- Anderson G.H., Jr., Blakeman N., Streeten D.H. (1994) The Effect of Age on Prevalence of Secondary Forms of Hypertension in 4429 Consecutively Referred Patients. *J Hypertens* 12: 609–615.
- Astuti D., Latif F., Dallol A., Dahia P.L., Douglas F., George E., et al. (2001) Gene Mutations in the Succinate Dehydrogenase Subunit Sdhb Cause Susceptibility to Familial Pheochromocytoma and to Familial Paraganglioma. *Am J Hum Genet* 69: 49–54
- Augoustides J.G., Abrams M., Berkowitz D., Fraker D. (2004) Vasopressin for Hemodynamic Rescue in Catecholamine-Resistant Vasoplegic Shock after Resection of Massive Pheochromocytoma. *Anesthesiology* 101: 1022–1024.
- Averbuch S.D., Steakley C.S., Young R.C., Gelmann E.P., Goldstein D.S., Stull R., et al. (1988) Malignant Pheochromocytoma: Effective Treatment with a Combination of Cyclophosphamide, Vincristine, and Dacarbazine. *Ann Intern Med* 109: 267–273.
- Baysal B.E., Ferrell R.E., Willett-Brozick J.E., Lawrence E.C., Myssiorek D., Bosch A., et al. (2000) Mutations in Sdhb, a Mitochondrial Complex II Gene, in Hereditary Paraganglioma. *Science* 287: 848–851.
- Bergman S.M., Sears H.F., Javadpour N., Keiser H.R. (1978) Postoperative Management of Patients with Pheochromocytoma. *J Urol* 120: 109–112.
- Bhatia K.S., Ismail M.M., Sahdev A., Rockall A.G., Hogarth K., Canizales A., et al. (2008) 123i-Metaiodobenzylguanidine (Mibg) Scintigraphy for the Detection of Adrenal and Extra-Adrenal Pheochromocytomas: Ct and Mri Correlation. *Clin Endocrinol (Oxf)* 69: 181–1888.
- Boutros A.R., Bravo E.L., Zanettin G., Straffon R.A. (1990) Perioperative Management of 63 Patients with Pheochromocytoma. *Cleve Clin J Med* 57: 613–617.
- Brain K.L., Kay J., Shine B. (2006) Measurement of Urinary Metanephrines to Screen for Pheochromocytoma in an Unselected Hospital Referral Population. *Clin Chem* 52: 2060–2064
- Brauckhoff M., Gimm O., Brauckhoff K., Dralle H. (2004) Repeat Adrenocortical-Sparing Adrenalectomy for Recurrent Hereditary Pheochromocytoma. *Surg Today* 34: 251.
- Bravo E.L. (1994) Evolving Concepts in the Pathophysiology, Diagnosis, and Treatment of Pheochromocytoma. *Endocr Rev* 15: 356–368.
- Bravo E.L., Tagle R. (2003) Pheochromocytoma: State-of-the-Art and Future Prospects. *Endocr Rev* 24: 539–553.
- Briggs R.S., Birtwell A.J., Pohl J.E. (1978) Hypertensive Response to Labetalol in Pheochromocytoma. *Lancet* 1: 1045–1046.
- Brouwers F.M., Eisenhofer G., Tao J.J., Kant J.A., Adams K.T., Linehan W.M., et al. (2006) High Frequency of Sdhb Germline Mutations in Patients with Malignant Catecholamine-Producing Paragangliomas: Implications for Genetic Testing. *J Clin Endocrinol Metab* 91: 4505–4509.
- Brunt L.M. (2001) Pheochromocytoma in Pregnancy. *Br J Surg* 88: 481–483.
- Bryant J., Farmer J., Kessler L.J., Townsend R.R., Nathanson K.L. (2003) Pheochromocytoma: The Expanding Genetic Differential Diagnosis. *J Natl Cancer Inst* 95: 1196–1204.
- Burnichon N., Briere J.J., Libe R., Vescovo L., Riviere J., Tissier F., et al. (2010) Sdhb Is a Tumor Suppressor Gene Causing Paraganglioma. *Hum Mol Genet* 19: 3011–3020
- Burnichon N., Vescovo L., Amar L., Libe R., De Reynies A., Venisse A., et al. (2011) Integrative Genomic Analysis Reveals Somatic Mutations in Pheochromocytoma and Paraganglioma. *Hum Mol Genet* 20: 3974–3985.
- Comino-Mendez I., Gracia-Aznarez F.J., Schiavi F., Landa I., Leandro-Garcia L.J., Leton R., et al. (2011) Exome Sequencing Identifies Max Mutations as a Cause of Hereditary Pheochromocytoma. *Nat Genet* 43: 663–667.
- Costello G.T., Moorthy S.S., Vane D.W., Dierdorf S.F. (1988) Hypoglycemia Following Bilateral Adrenalectomy for Pheochromocytoma. *Crit Care Med* 16: 562–563.
- Darr R., Eisenhofer G., Kotzerke J., Zophel K., Stroszczynski C., Deinum J., et al. (2011) Is There Still a Place for Adrenal Venous Sampling in the Diagnostic Localization of Pheochromocytoma? *Endocrine* 40: 75–79.
- Decoux M., Wemeau J.L., Racadot-Leroy N., Grimbert I., Proye C., Plane C. (1987) [Alpha-Methyl-Paratyrosine in the Treatment of Malignant Pheochromocytoma]. *Rev Med Interne* 8: 383–388
- Demeure M.J., Carlsen B., Traul D., Budney C., Lalande B., Lipinski A., et al. (1998) Laparoscopic Removal of a Right Adrenal Pheochromocytoma in a Pregnant Woman. *J Laparoendosc Adv Surg Tech A* 8: 315–31.
- Desmots J.M., Marty J. (1984) Anaesthetic Management of Patients with Pheochromocytoma. *Br J Anaesth* 56: 781–789.
- Douglas W.W., Rubin R.P. (1963) The Mechanism of Catecholamine Release from the Adrenal Medulla and the Role of Calcium in Stimulus-Secretion Coupling. *J Physiol* 167: 288–310.
- Eisenhofer G., Bornstein S.R., Brouwers F.M., Cheung N.K., Dahia P.L., De Krijger R.R., et al. (2004) Malignant Pheochromocytoma: Current Status and Initiatives for Future Progress. *Endocr Relat Cancer* 11: 423–436
- Eisenhofer G., Pacak K., Huynh T.T., Qin N., Bratslavsky G., Linehan W.M., et al. (2010) Catecholamine Metabolomic and Secretory Phenotypes in Pheochromocytoma. *Endocr Relat Cancer* 18: 97–111.
- Eisenhofer G., Timmers H.J., Lenders J.W., Bornstein S.R., Tiebel O., Mannelli M., et al. (2011a) Age at Diagnosis of Pheochromocytoma Differs According to Catecholamine Phenotype and Tumor Location. *J Clin Endocrinol Metab* 96: 375–384.
- Eisenhofer G., Lenders J.W., Timmers H., Mannelli M., Grebe S.K., Hofbauer L.C., et al. (2011b) Measurements of Plasma Methoxytyramine, Normetanephrine, and Metanephrine as Discriminators of Different Hereditary Forms of Pheochromocytoma. *Clin Chem* 57: 411–420
- Eisenhofer G., Lenders J.W., Siegert G., Bornstein S., Friberg P., Milosevic D., Mannelli M., Linehan W.M., Adams K., Timmers H., Pacak K. (2011c) Plasma Methoxytyramine: A Novel Biomarker of Metastatic Pheochromocytoma and Paraganglioma in Relation to Established Risk Factors of Tumor Size, Location and Sdhb Mutation Status. *Eur J Cancer*: in press Engelman K. (1977) Pheochromocytoma. *Clin Endocrinol Metab* 6: 769–797