World Journal of Environmental Biosciences

Available Online at: **www.environmentaljournals.org**

Volume 10, Issue 3: 18-22

https://doi.org/10.51847/tUlqbd3ivR

ISSN 2277- 8047

An Overview on Pheochromocytoma Diagnosis and Management Approach, Review Article

Yazeed Ali Aljabri[1*], Faris Sami Alghamdi[1], Khaled Ahmed Almehmadi[1], Abdulrahman Abubaker Babkoor[1], Abdulhafiz Muhammad Bahalaq[1], Anwar Aziz Althaqfi[1], Abdullah Ghazi Alharbi[1], Rayan Saud Alhazmi[1], Ahmad Ali Almalki[1]

[1]Faculty of Medicine, Umm Al Qura University, Makkah, KSA.

ABSTRACT

Pheochromocytoma is a neuroendocrine tumor that originates from a chromaffin cell located within the adrenal medulla. It is characterized by its ability to secrete catecholamines. Most cases are aged between 30-50 years and is affecting both sexes equally. It is relatively rare with incidence ranging from 2-8 cases per million. Most cases are due to sporadic mutation, but can also occur as part of other autosomal dominant familial disorders chiefly VHL syndrome, MEN2, and NF1. We aimed to review the literature regarding Pheochromocytoma clinical presentation and features in addition to the updated means of management. PubMed database was used for articles selection, and papers were obtained and reviewed. Pheochromocytoma can present in a wide variety of non-specific symptoms which can present a challenge for the early detection of patients. Some of the most common presentations include hypertension, headache, sweating, or palpitations. Treatment is surgical resection with proper pre-operative medical care. A minimally invasive approach using laparoscopic or robotic techniques is advised. Sporadic cases undergo total adrenalectomy while patients with familial disorder have partial adrenalectomy. Other modalities of treatment are reserved for irresectable or metastatic cases.

Keywords: *Pheochromocytoma, Neurofibromatosis 1, NF1, MEN syndrome*

Corresponding author: Yazeed Ali Aljabri
e-mail ✉ Yazeed.aljabri1@gmail.com
Received: 03 July 2021
Accepted: 30 Septembr 2021

INTRODUCTION

Pheochromocytoma is a neuroendocrine tumor characterized by its ability to secrete catecholamines, they originate from a chromaffin cell located within the adrenal medulla (Fang *et al.*, 2020), and are considered rare due to its low incidence ranging from 2-8 cases per million (Shrihari, 2019; Aygun & Uludag, 2020; Thieu *et al.*, 2020). Although, it can develop at any age the vast majority of cases are aged between 30-50 years, with only 10-20% of cases occurring in the pediatric population (Crona *et al.*, 2017; Aygun & Uludag, 2020), and it affects both sexes equally (Cerqueira *et al.*, 2020). Most of these tumors are sporadic, but around 40% of cases occur as part of other autosomal dominant familial disorders chiefly VHL syndrome, MEN2, and NF1 (Kantorovich & Pacak, 2018). In this paper review, we will go through the clinical presentation, features, and management of Pheochromocytoma.

MATERIALS AND METHODS

PubMed database was used for articles selection, and the following keys were used in the mesh (((Pheochromocytoma) AND (clinical picture)) OR (presentation)) OR (management). In regards to the inclusion criteria, the articles were selected based on the inclusion of one of the following topics; Pheochromocytoma, its presentation, clinical features, or management. Exclusion criteria were all other articles that did not have one of these topics as their primary endpoint.

Clinical presentation

Typically, patients were suspected to have Pheochromocytoma if they came complaining of typical symptoms and signs, or if they had a positive family history, but a rising number of cases are asymptomatic and are being discovered incidentally by identification of an adrenal mass with poor-lipid after undergoing computed scan or MRI for an unrelated reason (Tevosian & Ghayee, 2019).

One of the most challenging aspects of this disease is the early identification of the patients. This is because symptoms are merely present in only 50% of cases and are not highly specific (Martucci & Pacak, 2014) because they could be caused by a plethora of unrelated conditions, mainly diseases affecting the sympathetic system (Lenders & Eisenhofer, 2017). These symptoms could be caused either by catecholamines overproduction (adrenaline and noradrenaline mainly being the latter), local pressure, or metastasis (Farrugia, 2019). In addition, they usually occur in paroxysmal fashion (known as spills) due to episodic release of catecholamines, these spills occur at varying intervals ranging from multiple episodes per day to monthly fashion, and could also be brought upon by a triggering event such as applying pressure over the tumor,

extreme exertion, anxiety, consumption of foods containing tyramine like beers and cheese, use of certain drugs (histamine, glucagon, tyramine, phenothiazine, metoclopramide, adrenocorticotropic hormone), induction of anesthesia, chemotherapy, and endoscopy (Gupta *et al.*, 2017).

The widely known classical triad of Pheochromocytoma consists of episodes of headache, sweating, and palpitations, with headache being the most common complaint experienced in around 60% of symptomatic patients (Pourian *et al.*, 2015), followed by sweating occurring approximately in 59% of cases. However, having the full picture of the triad is not mandatory as it is absent in most cases around 76% (Cerqueira *et al.*, 2020). Patients may complain of pain as a direct effect of tumor size expansion or more dreadfully due to metastasis primarily to the bones (Gupta *et al.*, 2017). Other less common symptoms include palpitations, orthostatic hypotension, pallor, generalized weakness, and panic attack-type symptoms (Geroula *et al.*, 2019) Hypertension is the most common sign and is present in around half of the patients either in a paroxysmal or sustained form with the former being more common, (Tevosian & Ghayee, 2019) with only a minority of cases being normotensive around 10%. Long-standing hypertension can affect multiple organs leading to other complications ranging from, arrhythmias, strokes, or even renal failure (Domi & Laho, 2012).

The abundant catecholamines circulating in the bloodstream can have dire effects on the body, one of which is its interference with carbohydrate metabolism, leading to increased resistance of cells to insulin and the subsequent development of a clinical picture similar to type 2 diabetes, where patients complain of polyuria, polydipsia, increased blood glucose levels and weight loss (Pogorzelski *et al.*, 2014). One of the rare complications of catecholamines is its effect on the heart, which may lead to the development of cardiomyopathy and possible heart failure, after which patients may have pulmonary congestion and dyspnea, and if the patient received beta-blockers for symptomatic relief, it will usually have a counterproductive effect and will further worsen the symptoms (Gupta *et al.*, 2017). Another complication of this disease is known as Pheochromocytoma multisystem crisis can present with high-grade fever, in addition to altered mental status, multiorgan dysfunction, and either hyper or hypotension, but fortunately this hardly ever does occur (Kakoki *et al.*, 2015).

Management

Once the patient is diagnosed with Pheochromocytoma then he should undergo surgical resection of the tumor when possible, as it is regarded as the only curative modality. Before that, patients must have appropriate medical care as part of their preoperative preparation, to control the blood pressure, prevent volume depletion, avoid triggering events, and ultimately reduce and prevention of perioperative complications because failure to do so will usually result in dire consequences and could even be lethal (Cerqueira *et al.*, 2020).

Combined alpha and beta-adrenergic blockage

This approach is the most common method to control blood pressure and avoid perioperative complications such as hypertensive crises

Alpha-adrenergic blockage

Phenoxybenzamine a non-selective, irreversible, long-acting alpha-blocker is usually the drug of choice, due to its effect on blood pressure control and prevention of arrhythmias, it should be given for at least 7 days and ideally 14 days before surgery, but this duration should be increased in cases of recent MI, cardiomyopathy, refractory hypertension, and catecholamine-induced vasculitis. The first dose is 10mg and is then adjusted based on blood pressure levels and spills frequency. The adjustment should be gradual taking place every few days until reaching adequate response. Most patients will respond well to doses ranging from 20-100mg. Higher doses will predispose the patients to experience more side effects such as extreme fatigue, nasal stuffiness, retrograde ejaculation, tachycardia, dizziness, and orthostasis. Patients should be advised to increase daily sodium consumption (>5000) to counteract volume depletion which is the main culprit for some of these side effects (Lenders *et al.*, 2014; Fishbein, 2016).

Other alpha-blocker drugs such as prazosin are usually indicated when prolonged pharmacological treatment is desired, due to fact that they are cheaper, could be tittered more quickly have better side effects if compared to phenoxybenzamine which includes vertigo, dizziness, headache, GI upset, and Postural hypotension (Lenders *et al.*, 2014).

Beta-adrenergic blockage

A Beta-adrenergic blockage is used mainly to control the heart rate and prevent tachycardia examples include propranolol and metoprolol with the latter being more preferred due to its cardiac selectivity, a key point to keep in mind that they should never be initiated before alpha-blockers and are usually initiated 3-4 days before surgery, as failure to do so will to unopposed alpha-receptor stimulation and subsequently extreme vasoconstriction. Thus, these patients will be prone to develop heart failure, pulmonary edema, or hypertensive crises, another precaution to take is assessing the patient's past medical history for co-morbid conditions like asthma and COPD in which beta-blockers are relatively contraindicated.

Labetalol has a dual blockage effect on both alfa and beta receptors, but it is not considered to be the first-line choice due to its unbalanced effect of 1:7 on alpha to beta receptors respectively, which may predispose the patients to Hypertensive crises or paradoxical hypertension episodes. In addition, labetalol interrupts the uptake of 131I-metaiodobenzylguanidine (131I-MIBG), which is an agent used in scintigraphy for the diagnosis and localization of PGLs, causing false-negative results. So, the patient should be instructed to stop it for at least 2 weeks before testing (Lenders *et al.*, 2014; Fishbein, 2016).

Calcium channel blockers

Calcium channel blockers are being used as alternative options for adrenergic-blockers in the prevention of hypertension and tachyarrhythmias in cases of intolerance due to side effects mainly orthostatic hypotension. Additionally, they also could be used as an add-on therapy to cases with inadequate blood pressure control despite using alpha-blockers. For instance, Amlodipine could be given with a dose of 5–10 mg/day, while nicardipine from 60–120 mg/day (Fishbein, 2016).

Metyrosine

Tyrosine hydroxylase is an enzyme that plays a role in the first step of catecholamine production. Metyrosine acts by inhibition of this enzyme leading to decreased synthesis of catecholamine. Its main drawback is being very expensive therefore is usually reserved for patients with metastatic or large tumors with overwhelming catecholamine build-ups.

The usual regimen is to start 1–3 weeks preoperative, with 250 mg every 6-8 hours and is titrated as necessary with 250 mg increments up to 4 g per day, during which patients should be advised to increase their fluid intake to more than 2 liter/day to prevent crystalluria, other side effects primarily involve the nervous system, due to its ability to cross the blood-brain barrier and preventing catecholamine synthesis, leading to sedation, depression, anxiety, lethargy GI disturbance, and extrapyramidal effects. That is why the concomitant use of haloperidol or other typical antipsychotics should be avoided. (McBride *et al.*, 2011; Butz *et al.*, 2017)

Adrenalectomy

Tumor resection is the procedure of choice for patients with pheochromocytoma and should be performed for all eligible cases, especially for single, small tumors confined to the adrenal medulla and without any radiological evidence of malignancy. A minimally invasive approach through laparoscopic or robotic intervention is desirable due to similar outcomes to put better post-operative complications and shorter recovery in comparison to open surgery as it can be successfully performed safely in around 90% of the patients. But it should only be done in the hands of capable endocrine surgeons with sufficient expertise in the procedure. Otherwise, lethal errors can occur during the surgery such as retroperitoneal spread due to rupture of the tumor capsule. There is some evidence that the retroperitoneal approach is superior to transabdominal but it is not concrete and requires more research. (Nehs & Ruan, 2011; Aliyev *et al.*, 2013; Nomine-Criqui *et al.*, 2015; Bihain *et al.*, 2020)

A key difference between sporadic cases and patients with a familial disorder is that the latter has a high risk of bilateral disease unlike the former. Therefore, in sporadic cases, we opt for complete removal of the adrenal because the vast majority are unilateral. On the other hand, in patients with a genetic disorder or bilateral disease, the optimal choice is partial adrenalectomy by removing the medulla and sparing the cortex to avert the patient from glucocorticoid deficiency in the future. (Cerqueira *et al*., 2020)

As for metastatic disease, tumor resection of both the primary tumor and metastasis whenever possible can be either curative or palliative. Unfortunately, only in a very small fraction of cases does it play a curative role, while in the majority of patients, it is performed to decrease tumor size and catecholamine level, which offer some degree of symptomatic relief and increase in survival chance when combined with other modalities of treatment (Ellis *et al*., 2013) such as Transarterial chemoembolization for liver metastasis, radiofrequency ablation with dose >40 gammas for tumors in the skull base, neck, or bone. But this is still an evolving topic with newly emerging treatments, and won't be part of this paper scope.

Systemic treatment

Systemic Radionuclide treatment

It works by delivering beta-emitting isotopes to the tumor cells by attaching them to either MIBG or somatostatin analogs. (Cerqueira *et al*., 2020) MIBG which stands for iobenguane i-131, is the most studied systemic treatment, has both diagnostic and therapeutic effects, and this is achieved principally due to its shape similarity to NE, and therefore, is readily being absorbed by chromaffin cells, one meta-analysis showed that 3% had complete remission. While, there was a partial response in 27% of patients and a static course in 52% of cases, but this percentage diminishes significantly if combined or used after external beam radiation, as it causes the cells to lose their ability to absorb the MIBG post-radiation. The main disadvantage of this treatment arises from its partial specificity leading to it being absorbed by other tissues particularly the bone marrow, which is reflected by having hematologic toxicity with grade 3–4 neutropenia in 87% of patients (Gonias *et al*., 2009).

Neuroendocrine tumors including Pheochromocytoma share similar features, one of which is their expression of somatostatin receptors. Fortunately, this serves as a route for Radionuclide delivery to the tumor using analogues for example ^{90}Y-edotreotide, ^{90}Y-dotatoc, and is considered a safe and effective treatment for Pheochromocytoma (Satapathy *et al*., 2019).

Another newly experimented treatment is the use of octreotide (a somatostatin analogue) in the treatment of metastatic Pheochromocytoma, and it showed mixed results ranging from hormonal release inhibition and tumor growth attenuation to having no effect, and no unified consensus could be based on it. Thus, further research is warranted (Boedeker, 2011).

Chemotherapy, immunotherapy, and targeted therapy

These modalities could be used as 3rd or 4th line of management in patients with an overwhelming or a rapidly progressive metastatic tumor, where the aforementioned treatment was futile. The most studied chemotherapy regime (known as CVS), which consist of cyclophosphamide, vincristine, and dacarbazine, have shown moderate effect with 4% remission, a partial response in 37%, and stable disease in 14%, but on the other hand, multiple and severe side effect where experienced by the patients ranging from N&V, bone marrow failure, autonomic neuropathy, and infertility (Cerqueira *et al*., 2020).

As for targeted and immunotherapy using Sunitinib, Tyrosine kinase inhibitors (Cabozantinib), axitinib, lenvatinib, and pazopanib, all of these drugs are still undergoing clinical trial and present future treatment and hope for patients with Pheochromocytoma (Cerqueira *et al*., 2020).

CONCLUSION

Pheochromocytoma is a rare neuroendocrine tumor originating from a chromaffin cell found within the adrenal medulla. The most common etiology is a sporadic mutation or part of familial disorders like MEN2 and VHL syndrome. Symptoms are the result of excessive catecholamine production, which most patients develop hypertension, headache, sweating, or palpitations. These symptoms do not tend to persist but rather have episodic nature. Some patients are asymptomatic and are discovered incidentally through imaging. The gold standard treatment is multidisciplinary chiefly by surgical resection with proper pre-operative medical care. The preoperative

preparation is aimed to decrease perioperative morbidity and mortality through administration of dual adrenergic blockade with or without CCB and metyrosine, surgical resection is recommended to happen through a minimally invasive approach using laparoscopic or robotic techniques, sporadic cases undergo total adrenalectomy while patients with the familial disorder have partial adrenalectomy, radionucleotides treatment with MIBG or somatostatin are considered to be 2nd line of therapy and are mainly used if surgery is not possible or for treatment of metastatic disease, other modalities of emerging treatments like octreotide and immunotherapy are still been evaluated and present hope for future treatments.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

REFERENCES

Aliyev, S., Karabulut, K., Agcaoglu, O., Wolf, K., Mitchell, J., Siperstein, A., & Berber, E. (2013). Robotic versus laparoscopic adrenalectomy for pheochromocytoma. *Annals of Surgical Oncology*, *20*(13), 4190-4194.

Aygun, N., & Uludag, M. (2020). Pheochromocytoma and paraganglioma: from epidemiology to clinical findings. *The Medical Bulletin of Sisli Etfal Hospital*, *54*(2), 159-168.

Bihain, F., Klein, M., Nomine-Criqui, C., & Brunaud, L. (2020). Robotic adrenalectomy in patients with pheochromocytoma: a systematic review. *Gland Surgery*, *9*(3), 844-848.

Boedeker, C. C. (2011). Paragangliomas and paraganglioma syndromes. *GMS Current Topics in Otorhinolaryngology, Head and Neck Surgery. 10*:Doc03.

Butz, J. J., Weingarten, T. N., Cavalcante, A. N., Bancos, I., Young Jr, W. F., McKenzie, T. J., Schroeder, D. R., Martin, D. P., & Sprung, J. (2017). Perioperative hemodynamics and outcomes of patients on metyrosine undergoing resection of pheochromocytoma or paraganglioma. *International Journal of Surgery*, *46*, 1-6.

Cerqueira, A., Seco, T., Costa, A., Tavares, M., & Cotter, J. (2020). Pheochromocytoma and Paraganglioma: A Review of Diagnosis, Management and Treatment of Rare Causes of Hypertension. *Cureus*, *12*(5), e7969.

Crona, J., Taïeb, D., & Pacak, K. (2017). New perspectives on pheochromocytoma and paraganglioma: toward a molecular classification. *Endocrine Reviews*, *38*(6), 489-515.

Domi, R., & Laho, H. (2012). Management of pheochromocytoma: old ideas and new drugs. *Nigerian Journal of Clinical Practice*, *15*(3), 253-257.

Ellis, R. J., Patel, D., Prodanov, T., Sadowski, S., Nilubol, N., Adams, K., Steinberg, S. M., Pacak, K., & Kebebew, E. (2013). Response after surgical resection of metastatic pheochromocytoma and paraganglioma: can postoperative biochemical remission be predicted?. *Journal of the American College of Surgeons*, *217*(3), 489-496.

Fang, F., Ding, L., He, Q., & Liu, M. (2020). Preoperative management of pheochromocytoma and paraganglioma. *Frontiers in Endocrinology*, *11*, 783.

Farrugia, F. A. (2019). Charalampopoulos A. Pheochromocytoma. *Endocrine Regulations, 53*(3), 191-212.

Fishbein, L. (2016). Pheochromocytoma and paraganglioma: genetics, diagnosis, and treatment. *Hematology/Oncology Clinics*, *30*(1), 135-150.

Geroula, A., Deutschbein, T., Langton, K., Masjkur, J., Pamporaki, C., Peitzsch, M., Fliedner, S., Timmers, H. J., Bornstein, S. R., Beuschlein, F., et al. (2019). Pheochromocytoma and paraganglioma: clinical feature-based disease probability in relation to catecholamine biochemistry and reason for disease suspicion. *European Journal of Endocrinology*, *181*(4), 409-420.

Gonias, S., Goldsby, R., Matthay, K. K., Hawkins, R., Price, D., Huberty, J., Damon, L., Linker, C., Sznewajs, A., Shiboski, S., et al. (2009). Phase II study of high-dose [131I] metaiodobenzylguanidine therapy for patients with metastatic pheochromocytoma and paraganglioma. *Journal of Clinical Oncology*, *27*(25), 4162-4168.

Gupta, G., Pacak, K., & AACE Adrenal Scientific Committee. (2017). Precision medicine: an update on genotype/biochemical phenotype relationships in pheochromocytoma/paraganglioma patients. *Endocrine Practice*, *23*(6), 690-704.

Kakoki, K., Miyata, Y., Shida, Y., Hakariya, T., Takehara, K., Izumida, S., Sekino, M., Kinoshita, N., Igawa, T., Fukuoka, J., et al. (2015). Pheochromocytoma multisystem crisis treated with emergency surgery: a case report and literature review. *BMC Research Notes*, *8*(1), 758.

Kantorovich, V., & Pacak, K. (2018). New insights on the pathogenesis of paraganglioma and pheochromocytoma. *F1000Research*, *7*.

Lenders, J. W., & Eisenhofer, G. (2017). Update on modern management of pheochromocytoma and paraganglioma. *Endocrinology and Metabolism*, *32*(2), 152-161.

Lenders, J. W., Duh, Q. Y., Eisenhofer, G., Gimenez-Roqueplo, A. P., Grebe, S. K., Murad, M. H., Naruse, M., Pacak, K., & Young Jr, W. F. (2014). Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, *99*(6), 1915-1942.

Martucci, V. L., & Pacak, K. (2014). Pheochromocytoma and paraganglioma: diagnosis, genetics, management, and treatment. *Current Problems in Cancer*, *38*(1), 7-41.

McBride, J. F., Atwell, T. D., Charboneau, W. J., Young Jr, W. F., Wass, T. C., & Callstrom, M. R. (2011). Minimally invasive treatment of metastatic pheochromocytoma and paraganglioma: efficacy and safety of radiofrequency ablation and cryoablation therapy. *Journal of Vascular and Interventional Radiology*, *22*(9), 1263-1270.

Nehs, M. A., & Ruan, D. T. (2011). Minimally invasive adrenal surgery: an update. *Current Opinion in Endocrinology, Diabetes and Obesity*, *18*(3), 193-197.

Nomine-Criqui, C., Brunaud, L., Germain, A., Klein, M., Cuny, T., Ayav, A., & Bresler, L. (2015). Robotic lateral transabdominal adrenalectomy. *Journal of Surgical Oncology*, *112*(3), 305-309.

Pogorzelski, R., Toutounchi, S., Krajewska, E., Fiszer, P., Łykowski, M., Zapała, Ł., Szostek, M., Jakuczun, W., Pachucki, J., & Skórski, M. (2014). The effect of surgical treatment of phaeochromocytoma on concomitant arterial hypertension and diabetes mellitus in a single–centre retrospective study. *Central European Journal of Urology*, *67*(4), 361-365.

Pourian, M., Mostafazadeh, D. B., & Soltani, A. (2015). Does this patient have pheochromocytoma? A systematic review of clinical signs and symptoms. *Journal of Diabetes & Metabolic Disorders*, *15*(1), 1-12.

Satapathy, S., Mittal, B. R., & Bhansali, A. (2019). Peptide receptor radionuclide therapy in the management of advanced pheochromocytoma and paraganglioma: A systematic review and meta-analysis. *Clinical Endocrinology*, *91*(6), 718-727.

Shrihari, T. G. (2019). Chronic Inflammatory Mediators in Tumor Microenvironment Induced Tumor Progression. *International Journal of Pharmaceutical and Phytopharmacological Research , 9*(2), 28-31.

Tevosian, S. G., & Ghayee, H. K. (2019). Pheochromocytomas and paragangliomas. *Endocrinology and Metabolism Clinics*, *48*(4), 727-750.

Thieu, H. H., Lao, T. D., & Le, T. A. H. (2020). Characterization of Promoter Hypermethylation of Tumor Suppressor Gene Rassf1a and its Association with The Risk of Nasopharyngeal Carcinoma. *Pharmacophore, 11*(3), 56-62.