

2019

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Recommended Citation

Manea, Maria; Marcu, Dragos R.; Bratu, Ovidiu G.; Stanescu, Ana M.; Pantea Stoian, Anca; Gaman, Mihnea A.; and Diaconu, Camelia C. (2019) "Pheochromocytoma – clinical manifestations, diagnosis and current perioperative management," *Journal of Mind and Medical Sciences*: Vol. 6 : Iss. 2 , Article 10.

DOI: 10.22543/7674.62.P243247

Available at: <https://scholar.valpo.edu/jmms/vol6/iss2/10>

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Received for publication: June 22, 2019
Accepted: August 14, 2019

Review

Pheochromocytoma – clinical manifestations, diagnosis and current perioperative management

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Abstract

Pheochromocytoma is a neuroendocrine tumor characterized by the excessive production of catecholamines (epinephrine, norepinephrine, and dopamine). The diagnosis is suspected due to hypertensive paroxysms, associated with vegetative phenomena, due to the catecholaminergic hypersecretion. Diagnosis involves biochemical tests that reveal elevated levels of catecholamine metabolites (metanephrine and normetanephrine). Functional imaging, such as 123I-metaiodobenzylguanidine scintigraphy (123I-MIBG), has increased specificity in identifying the catecholamine-producing tumor and its metastases. The gold-standard treatment for patients with pheochromocytoma is represented by the surgical removal of the tumor. Before surgical resection, it is important to optimize blood pressure and intravascular volume in order to avoid negative hemodynamic events.

Keywords

: catecholamines, hypertensive paroxysm, metanephrine, normetanephrine, alpha-receptors blockade

Highlights

- ✓ The gold-standard treatment in patients diagnosed with pheochromocytoma is the surgical removal of the tumor. Preoperative preparation is very important and its goal is to decrease the incidence of intraoperative cardiovascular complications.
- ✓ The incidence of morbidity and mortality associated with the surgical removal of these tumors has decreased recently, considering the careful and prompt management in the perioperative period and the advancements of the surgical technique.

To cite this article: Manea M, Marcu DR, Bratu OG, Stanescu AMA, Stoian AP, Gaman MA, Diaconu CC. Pheochromocytoma – clinical manifestations, diagnosis and current perioperative management. *J Mind Med Sci.* 2019; 6(2): 243-247. DOI: 10.22543/7674.62.P243247

Introduction

Pheochromocytoma is a neuroendocrine tumor derived from the chromaffin cells of the medullary portion of the adrenal glands, being characterized by the excessive production and release of catecholamines (adrenaline and noradrenaline) (1). Paraganglioma is also a catecholamine producing tumor, but with extra-adrenal localization (2). The most important clinical manifestation of pheochromocytoma is the hypertensive crisis due to the tumoral secretion of catecholamines (1). Surgical removal of the tumor represents the treatment of choice in order to cure and prevent cardiovascular complications (3).

Discussions

Epidemiology and etiology

Pheochromocytoma occurs with equal frequency in men and women, and it can occur at any age (4). In 20% of the cases, pheochromocytoma has a hereditary transmission, with bilateral localization (3). 10% of the cases of pheochromocytoma are malignant, and paraganglioma occurs in 10-15% of the cases (5). A genetic component has been identified in 30% of the cases of pheochromocytoma, being associated with Von Hippel-Lindau disease, with neurofibromatosis, and with multiple endocrine neoplasia type 1 and type II syndrome (MEN I and MEN II) (6). The etiology of pheochromocytoma is represented by increased tumoral production and the secretion of catecholamines (4).

Pathophysiology

The pathophysiological mechanism underlying pheochromocytoma is represented by the increased release of catecholamine hormones, secreted by the tumor, continuously or in an episodic manner. These hormones, which include epinephrine, norepinephrine, and dopamine, excessively stimulate alpha- and beta-adrenergic receptors, with all the clinical manifestations in pheochromocytoma being related to this (7).

The symptomatology in pheochromocytoma is given by the predominant type of catecholaminergic secretion. Epinephrine stimulates beta-1 and beta-2 adrenergic receptors. By stimulating beta-2 adrenergic receptors, epinephrine causes vasodilation in striate muscles. Also, epinephrine has metabolic effects, stimulating hepatic glycogenolysis and gluconeogenesis, thus leading to hyperglycemia (8). Norepinephrine stimulates alpha-1, alpha-2, and beta-2 adrenergic receptors, leading to vasoconstriction and increased blood pressure. Epinephrine and norepinephrine have positive chronotropic effects through their action on beta-1

adrenergic receptors (9). Dopamine stimulates dopaminergic receptors D1 and D2. In cases of pheochromocytoma, dopamine concentrations are elevated, thus causing vasoconstriction and increased heart rate (10). Moreover, pheochromocytoma is characterized by the release of other substances, such as neuron-specific enolase, vasoactive intestinal peptide, or adrenocorticotrophic hormone (ACTH), which cause various other clinical manifestations (9).

Clinical presentation

The classical manifestation in pheochromocytoma is represented by the hypertensive crisis, associated with palpitations and diaphoresis, these symptoms being the result of the massive release of catecholaminergic hormones from the tumor. This symptomatology is present in 40% of the patients with pheochromocytoma (11). The hypertensive paroxysm can be triggered by different type of stress, such as surgery or anesthetics, intense physical effort, smoking, or palpation of the lumbar region (12).

The hypertensive crisis may last from a few minutes to a few hours. The end of the hypertensive paroxysm is characterized by arterial hypotension. The crisis is also associated with various symptoms, such as headache, diaphoresis, and heart rhythm disorders, these manifestations supporting the positive diagnosis of pheochromocytoma. Also, anxiety, visual disturbances, nausea, chest pain, or abdominal pain are associated with hypertensive paroxysm (13).

The effects of severe hypertension are quantified in lesions of the end-organs, especially the heart, kidney, eyes, and central nervous system. Also, hypertensive paroxysm can be associated with the signs and symptoms of hypertensive encephalopathy (such as an altered state of consciousness and convulsions) and acute myocardial ischemia due to the increased oxygen demand (14). Other clinical manifestations occur in pheochromocytoma due to the release of neuropeptides. Thus, the hypersecretion of ACTH leads to the occurrence of the signs and symptoms of hypercorticism. Also, the hypersecretion of calcitonin leads to hypocalcemia (15). Pheochromocytoma in genetic syndromes can be associated with other clinical signs, such as café-au-lait skin spots (13).

Diagnosis

When pheochromocytoma is suspected, the levels of catecholamines and their metabolites should be tested, such as metanephrines and normetanephrines. A rise in the plasma levels of metanephrines is an indicator of increased tumoral production and release of catecholamines. This diagnostic test has both high sensitivity and specificity.

Measurement of urinary metanephrines is also a test with high sensitivity in the diagnosis of pheochromocytoma (16). The measurement of plasmatic and urinary vanillylmandelic acid (VMA) is a test used for the diagnosis of these tumors (15).

Methoxytyramine is a marker used in the identification of malignant forms of pheochromocytoma. Also, chromogranin A is a marker of the presence of neuroendocrine tumors (17). The imaging evaluation (computed tomography [CT] and magnetic resonance imaging [MRI]) is important in establishing the localization and the dimensions of the tumor and also in identifying metastatic lesions. MRI describes the anatomical details and the vascular structures more clearly, but it does not identify small dimension tumors (18). Functional imaging using radiotracers such as ¹²³I-metaiodobenzylguanidine scintigraphy (¹²³I-MIBG) and ¹¹¹In-DTPA-pentetreotide scintigraphy has increased specificity in identifying the catecholamine-producing tumors and their metastases (19). Also, genetic tests are required in patients with a family history of pheochromocytoma (17).

Preoperative preparation

Pheochromocytoma is associated with end-organ lesions as a result of the excess of catecholamines. In this context, the surgical removal of these tumors is recommended in order to cure and prevent the lesions. Chai et al. observed that in patients diagnosed with pheochromocytoma, open transperitoneal adrenalectomy is the gold standard treatment (18). Nevertheless, due to the constant technological developments and also the need for less invasive surgery, the laparoscopic approach has become more popular over time. Before surgical resection, it is important to optimize the blood pressure and the intravascular volume as steps to avoid the negative hemodynamic events during surgery (20).

The need for preoperative antihypertensive therapy has been studied in patients with pheochromocytoma (21). In a retrospective study by Pogorzelski et al. from 2006 – 2012 that included 67 patients diagnosed with pheochromocytoma, a regression of arterial hypertension after surgical treatment of the tumor was noticed (22). Recent evidence shows that preoperative preparation with antihypertensive therapy decreases intra- and postoperative cardiovascular complications (23). The Endocrine Society Clinical Guidelines Subcommittee recommends preoperative alpha-blockade in patients undergoing the resection of the pheochromocytoma (22).

Guidelines indicate that preoperative preparation for the surgical removal of pheochromocytoma requires 5-15

days of the administration of alpha-receptor blockers and methods to increase the intravascular volume (20). The purpose of the preoperative preparation is to control the blood pressure for at least 3-5 days, with a systolic blood pressure under 130 mmHg and a diastolic value under 80 mmHg (24).

The main cause of hypertension in patients with pheochromocytoma is the alpha-receptor activation due to the excess of catecholamines. In this context, the first line therapy is represented by alpha-receptor antagonists. Also, beta-receptor antagonists and calcium channel blockers are used (25).

Prazosin, doxazosin, and terazosin are selective alpha-1 receptor antagonists. These drugs act on the alpha-1 receptors and produce vasodilation. The antagonism produced by these drugs is reversible (24). Prazosin is most frequently used in patients with indications of surgical resection of pheochromocytoma. Doses of prazosin are gradually increased, depending on the hypotensive response of the patient. Studies revealed a good perioperative control and adequate alpha-blockade in patients with pheochromocytoma (26). Doxazosin and terazosin are alternatives to prazosin, which is most commonly used.

Beta-blockers should not be administered before the initiation of alpha-receptor antagonists because the antagonism of beta-receptors can lead to acute cardiac failure and pulmonary edema. Beta-blockers are administered only after the initiation of alpha-receptor blockers (22). Cardio selective beta-blockers are more frequently used because this class has fewer side-effects. The most commonly used beta-receptor antagonists in patients with pheochromocytoma with indication for resection are metoprolol, atenolol, bisoprolol, carvedilol, propranolol (which is a non-selective beta-blocker), and labetalol. Labetalol has effects of alpha- and beta-receptor antagonism (27).

Calcium channel blockers can be administered as primary drugs in order to control hypertension or as adjunct antihypertensive therapy. Guidelines recommend these drugs especially for the control of blood pressure in patients with hypertensive paroxysms (23). The most commonly used calcium channel blockers are amlodipine, nifedipine, verapamil, and diltiazem (28).

Goldstein et al. highlighted the importance of alpha-blockade in patients diagnosed with pheochromocytoma with indication for the surgical removal of the tumor. They found 69% of the patients without alpha-blockade experienced perioperative cardiovascular complications, compared to 3% of the patients who received alpha-

blockers and did not experience intraoperative cardiovascular complications (26). Because the administration of alpha-receptor blockers can cause severe orthostatic hypotension, increasing intravascular volume with intravenous crystalloids and colloids is recommended (25).

Intraoperative drugs used in cases of hypertensive paroxysm are sodium nitroprusside and nitroglycerine (28). Also, esmolol is a beta-receptor blocker used intraoperatively to control hypertension and tachycardia (29). Intraoperative hypertension and hemodynamic instability occur depending on anesthetic drugs, tumoral dimensions, and plasma catecholamine levels (30).

Many studies report that postoperative hypotension has an incidence of 20-70% and is associated with the administration of the alpha-receptor antagonists before surgery and hypotensive agents administered during the surgical intervention (31, 32). Also, hyperinsulinemia and hypoglycemia may be noticed after the removal of the tumor.

After the surgical resection of the tumor, the values of blood pressure will normalize. Also, the values of the catecholamine metabolites will be within normal limits. Guidelines recommend that postoperative follow-up should occur through a three-month assessment period (33).

Conclusions

The clinical manifestations of pheochromocytoma may vary. The classical manifestation is represented by hypertensive paroxysm, associated with a vegetative phenomenon, such as palpitations or diaphoresis. CT scans represent the best functional imaging tests. Also, MRI scans may be used in cases of metastases or when radiation is to be avoided.

The gold-standard treatment in patients diagnosed with pheochromocytoma is the surgical removal of the tumor. Preoperative preparation is very important and its goal is to decrease the incidence of intraoperative cardiovascular complications. The first-line treatment is represented by alpha-receptor antagonists, especially selective ones (alpha-1 receptor antagonists). Also, beta-receptor antagonists and calcium channel blockers are used as adjunct antihypertensive therapy. The vascular volume replacement with fluids administered intravenously is recommended to avoid hypotension, which is the most common complication after tumor removal. The incidence of morbidity and mortality associated with the surgical

removal of these tumors has decreased recently, considering the careful and prompt management in the perioperative period and the advancements of the surgical technique.

Acknowledgements

All authors have contributed equally to this paper.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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