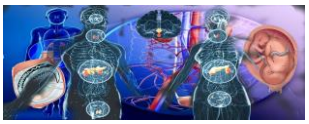
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Preoperative Management of Neuroendocrine Tumors: Pheochromocytoma

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Abstract

Pheochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumors, characterized by excessive release of catecholamines (CAs), and manifested as the classic triad of headaches, palpitations, profuse sweating, and a variety of other signs and symptoms. The diagnosis of PPGL requires both evidence of excessive release of CAs and anatomical localization of CA-secreting tumor. Surgery is the mainstay of treatment for all patients with PPGL unless contraindicated. However, without proper preparation, the release of excessive Cas.

Keywords: Catecholamine; paraganglioma; glossopharyngeal nerves; epinephrine-E

Introduction

A pheochromocytoma is a tumor derived from catecholamine (CA)-producing chromaffin cells in the adrenal medulla, while a paraganglioma is a tumor arising from extra-adrenal chromaffin cells. Since the two tumor types have similar histologic characteristics, they can only be differentiated by anatomical location (intra-adrenal or extra-adrenal). Sympathetic paragangliomas (CAs-producing) derive from paravertebral ganglia of thorax, abdomen, and pelvis, while parasympathetic paragangliomas (rarely produce CAs) arise from vagal and glossopharyngeal nerves at the base of skull and in the neck. Pheochromocytoma and paraganglioma are together referred to as PPGL. Approximately 80%–85% of PPGL are pheochromocytomas, while about 15%–20% are paragangliomas. The prevalence of PPGL is about 6 cases per 1 million person-years.

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.

PHEO and PGL are tumors that produce catecholamines (adrenaline, norepinephrine and dopamine). Often, production and catecholamine secretion are episodic and variable; with the excessive production and secretion of both noradrenaline (NA) and adrenaline, there is usually a predominance of NA. In less often cases, these can also be produced in isolation, and excess dopamine production rarely occurs. For this reason, PHEO and PGL are tumors with an extremely variable clinical presentation and may present a myriad of signs and symptoms, ranging from a complete lack of symptoms to cases of sudden death. They are characterized by the classic triad of features composed of headache, diaphoresis and tachycardia (with or without palpitations).

Diagnosis is made through a combination of laboratory and imaging tests. PHEO and PGL are diagnosed through the analytical evidence of excessive production of catecholamines or their metabolites. Adrenaline and norepinephrine are metabolized by catecholamine-O-methyl transferase in metanephrine and normetanephrine, respectively (inactive metabolites). The production and secretion of catecholamines by the tumor is often reduced and episodic in character, unlike that of its inactive metabolites whose production is performed continuously, by a process that is independent of exocytic secretion of catecholamines. Consequently, metanephrine measurement in both plasma and urine is an excellent diagnostic method and is currently recommended as an initial method of diagnosis, according to the recommendations of clinical practice of the Society of Endocrinology.

Preoperative Management of PPGL

PPGL is characterized by hypertension and low blood volume, resulting from excessive concentration of CAs in the plasma. With insufficient preoperative antihypertensive management or untreated hypovolemia, the hemodynamic instability during surgical treatment of PPGL may be lethal. Therefore, preoperative management, which includes hypertension control and expansion of blood volume, is extremely important. The main goal of preoperative management of PPGL is to normalize blood pressure and heart rate, restore effective circulating blood volume, improve metabolic condition, and prevent a patient from CA storm and hemodynamic instability during surgery.

α-AR Antagonists

Two types of α-AR antagonists are widely used clinically, non-selective and selective α-AR antagonists. Phenoxybenzamine is a non-selective, non-competitive α-AR antagonist, which binds irreversibly with both α1 and α2-AR. Phenoxybenzamine is long-acting and its effects persist long after it has been discontinued, since the effect diminishes only after α-AR resynthesis

Non-Selective or Selective α-AR Antagonists?

Evidence from RCTs or systematic reviews comparing the effectiveness of non-selective and selective α-AR antagonists for patients of PPGL is unavailable. However, many retrospective and prospective studies have made efforts to compare these two types of drugs. Some studies show that

non-selective α-AR antagonists, phenoxybenzamine, and selective α-AR antagonist, doxazosin, have similar effects on controlling blood pressure.

Is α-AR Blockade Necessary for All Patients of PPGL?

Many retrospective studies have reported the use α-AR antagonists as the first-choice to prevent perioperative complications of PPGL, including intraoperative hypertension, tachycardia, and hemodynamic instability. North American neuroendocrine tumor society consensus guidelines recommended that all patients with PPGL (even those with normal levels of CAs) should use appropriate management to block effects of released CAs.

β-AR Antagonists

The use of β-AR antagonists is determined by the extent of CA-induced tachycardia or reflex tachycardia after the initiation of phenoxybenzamine. It is noteworthy that β-AR antagonists should never be treated alone or before adequate α-AR blockade. Since for patients with PPGL, loss of β-AR-mediated vasodilatation with unopposed CA-induced vasoconstriction can cause dramatic increase in blood pressure, or even hypertensive crisis.

Calcium Channel Blockers (CCBs)

CCBs are the most commonly used drugs, in combination with α-AR antagonists, to further improve blood pressure control in patients with PPGL. Some studies consider this kind of drugs as the primary choice of preoperative management of PPGL, especially for normotensive patients or those with very mild hypertension, and for patients experiencing severe side effects with α-AR antagonists. These drugs can relax vascular smooth muscle and reduce peripheral vascular resistance by inhibiting NE-induced intracellular and transmembrane calcium influx in vascular smooth muscle.

Cardiovascular Evaluation and Blood Volume Restoration

The excessive CAs release and resultant hypertension can lead to significant changes in the cardiovascular system, such as vasoconstriction of the coronary arteries, increased arterial stiffness, arrythmias, and cardiomyopathy. Moreover, it was shown that normotensive patients with PPGL had similar perioperative hemodynamic instability to those with significant preoperative hypertension. Therefore, it is essential to perform cardiovascular evaluation for every patient with PPGL. The evaluation should include a thorough history, physical examination, complete laboratory tests, electrocardiogram (ECG), and echocardiography. An ECG may reveal pathologic findings such as nonspecific ST-T wave changes, arrythmias, and signs of left ventricular hypertrophy, which may be related to the CA-induced coronary artery vasoconstriction that obstructs myocardial blood flow.

Management of Hypertensive Crisis

PPGL may cause potentially lethal hypertensive crisis due to the effects of the excessive released CAs. Hypertensive crisis is an acute, life-threatening situation associated with severe increase in blood pressure, requiring special attention. It is defined as a systolic blood pressure higher than 180 mmHg or a diastolic blood pressure higher than 120 mmHg, with or without acute target organ damage. Hypertensive crisis may develop as a consequence of postural changes, urination, emotional stress, and use of certain drugs which may provoke the release of Cas.

Conclusion

In summary, preoperative management of PPGL, which includes hypertension control and improvement of blood volume, is crucial. The most common approach is to block the function of excessive plasma CAs, and α-AR antagonists are the first choice. Hypertension may be slightly better controlled by non-selective α-AR antagonist, phenoxybenzamine, for some patients, at the cost of higher risk of postoperative hypotension and other side effects. While selective α-AR antagonist, doxazosin, is proved to have much less adverse effects, but is more likely to be used in combination with additional antihypertensive drugs.

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