

Pheochromocytoma

Definition of Disease

Pheochromocytomas are tumors originating from the chromaffin cells of the adrenal medulla resulting in adrenomedullary hyperfunction where catecholamine secretion is on a continual or episodic basis.

Detailed pathophysiology at cellular, tissue, organ, and system levels

Pheochromocytomas are independent- functioning tumors that causes excessive production of catecholamines, predominantly norepinephrine. Phenylethanolamine N-methyltransferase enzyme is present primarily in the adrenal medulla and organ of Zuckerkandle, converts norepinephrine to epinephrine. Hence, high levels of epinephrine are suggestive of pheochromocytoma in these organs. Increased levels of catecholamines causes over activity of the sympathetic nervous system (SNS). Norepinephrine is an alpha-adrenergic agonist that causes vasoconstriction, reflex bradycardia, sweating, pupillary dilation, impaired gastrointestinal motility, and decreased insulin secretion. Epinephrine acts on beta-1 receptors that increase the heart rate and myocardial contraction, subsequently increasing systolic blood pressure, cardiac output, and oxygen consumption. Pheochromocytomas can seldom secrete other neurohormones like dopamine, adrenocorticotrophic hormones, β -endorphins, and other substances that can confound clinical manifestations and differential diagnosis.

Genetics

Approximately nine out of ten pheochromocytomas are benign and usually arise sporadically, rather than genetically. Between 10% and 15% of cases are familial which is linked with neuroectodermal disorders (von Hippel-Lindau disease, von Recklinghausen's disease, tuberous sclerosis, Sturge-Weber syndrome or Carney's syndrome) or as a part of hereditary multiple endocrine neoplasia (MEN) 2A and 2B. In MEN-2, bilateral adrenal medullary hyperplasia (diffuse or nodular) is almost always present and leads to pheochromocytoma, which occurs in about 30-50% of patients. Significant adrenal medullary disease is greater in MEN-2B. C-cell disease precedes pheochromocytoma in almost 25% of the time. Subsequently, mutation analyses of the RET proto-oncogene on exons 10 and 11 can help screen patients for MEN-2.

Epidemiology

Pheochromocytomas are rare, with about five to eight cases diagnosed per million people a year. This condition can similarly affect both adult men and women 30-60 years of age. Ten percent affects children and adolescents most commonly in 11 and 12 year olds. Pheochromocytomas are usually benign although less than 10% are malignant and may metastasize to the lungs, liver, bones or paraaortic lymph nodes. True incidence in the general population is unknown although approximately 0.1% of 1% of the adult population with hypertension has pheochromocytoma.

Disease described

Pheochromocytomas are catecholamine-secreting (epinephrine and norepinephrine) tumors of the adrenal medulla. They normally develop from the chromaffin tissue of the interior adrenal gland. However, 10% of pheochromocytomas develop in extra-adrenal areas which are referred to as paragangliomas. They are most commonly found in the organ of Zuckerkandle at the distal aorta and aortic bifurcation, base of the skull, the spermatic cords and bladder. There is no standard staging system for pheochromocytoma although there are three categories: • Localized (benign) disease. • Regional disease. • Metastatic disease (common in extra-adrenal tumors).

Sign and Symptoms

About 5% of people with pheochromocytoma are asymptomatic related to nonfunctioning tumors. However, these tumors can be activated in response to stress such as surgery or trauma. Clinical manifestations are associated with chronic effects of catecholamine release in the body. Complaints of heat intolerance, weight loss and constipation are common as well as forceful palpitations, tremor and facial pallor. The 5 H's are used as tell-tale signs of pheochromocytoma:

- Hypertension due to increased peripheral vascular resistance (PVR) which can be persistent or paroxysmal
- Headache due to cerebral blood flow affectation from catecholamine level changes in the circulation, more occipital than temporal
- Hypermetabolism due to chronic stimulation of sympathetic receptors in adipocytes, hepatocytes and various tissues

- Hyperglycemia due to inhibition of insulin secretion by the pancreas
- Hyperhidrosis occurs due to increased metabolic activity

Symptoms can be spontaneous or induced by a variety of events, including the following:

- Strenuous physical activity
- Trauma
- Labor and delivery
- Anesthesia induction
- Surgery or other invasive procedures, including direct contact with the tumor (such as fine-needle aspiration)
- Ingestion of foods high in tyrosine (such as red wine, chocolate, beer, yogurt and cheese) and caffeine
- Voiding (rarely occurs, brought about by pressure on the bladder wall tumor) Pheochromocytomas are highly vascular and may rupture which may present as a sudden, unexplained drop in blood pressure, abrupt abdominal pain and rigidity.

Diagnosis

The diagnosis is initiated with biochemical testing of blood or urine for measurement of increased levels of catecholamines. Current guidelines from the National Comprehensive Cancer Network suggest testing for plasma-free metanephrine and normetanephrine, or for urine metanephrine, catecholamines, creatinine, and possibly dopamine.

Pharmacological tests may also be performed on hypertensive patients with likely clinical suspicion for pheochromocytoma with repetitively non-diagnostic urinary and plasma catecholamine levels. Pharmacologic tests may include the clonidine suppression test (which uses clonidine to inhibit central neurogenic mediated catecholamine release but not catecholamine released autonomously by pheochromocytoma) and the provocative stimulation tests (which uses Glucagon, metoclopramide, histamine, tyramine and naloxone to stimulate catecholamine secretion from pheochromocytomas).

After diagnosis has been established biochemically, localization is indicated to identify tumor site. This includes CT Scan, MRI and Meta-Iodo-Benzyl-Guanidine (MIBG). Fine needle aspiration biopsy of adrenal lesions has an accuracy of 80% to 90%. However, this procedure can trigger a hypertensive crisis in patients with pheochromocytomas and is more likely indicated for patients who have normal biochemical studies because patients with positive biochemical studies require excision despite the cytology results.

Treatment

Pheochromocytoma is a rare, life-threatening condition that requires immediate recognition and intervention such as aggressive preoperative treatment to reduce mortality. Surgery is the treatment of choice, the goal being to remove the entire or part of the adrenal gland or tumor. Laparoscopic removal is ideal as it positively affects postoperative morbidity, hospital length of stay, and cost. Chemotherapy can also be an adjunct to surgery. Open resection may be indicated for larger tumors or metastatic suspicion. Preoperative medical management is crucial and should be started at the time of diagnosis to avert potentially life-threatening cardiovascular complications (such as hypertensive crisis, myocardial infarction, arrhythmia and pulmonary edema), that can ensue as a consequence of excess catecholamine secretion during surgery. Alpha-adrenergic blockers (such as phenoxybenzamine, prazosin, terazosin, and doxazosin) are commonly used as well as beta-adrenergic blockers (such as metoprolol or propranolol) later on.

Management of unresectable or metastatic pheochromocytoma may include a combination of the following:

- Catecholamine blockade
- Surgery
- Chemotherapy
- Radiofrequency ablation
- Cryoablation
- Radiation therapy

For more information on the disease and its treatment options, visit <http://www.cancer.gov>

References

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