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Pheochromocytoma

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Pheochromocytoma arises from adrenal medulla, which actually comprises about 10 % of adrenal gland. Sympathochromaffin system is the major neuroendocrine system in the body, it contains 2 components. Symapthetic neurons and chromaffin cells in adrenal medulla.

The sympathochromaffin system and the parasympathetic nervous system comprise the autonomic nervous system.

Catecholamine synthesis, storage and inactivation

Cathechol nucleus is esenatially an dihydroxy phenyl ring. The catecholamines - dopamine (DA), norepinephrine (NE) and ephinephrine (E) are synthesized from tyrosine which is actively taken to neurons. Tyrosine is made from phenylalanine, an essential aminoacid.

Catecholamines are found in the adrenal medulla and in sympathetically innervated organs. Catecholamines are stored in electron-dense granules that also contain ATP, neuropeptides (e.g., adrenomedullin, corticotropin [ACTH], vasoactive intestinal polypeptide), calcium, magnesium, and chromogranins. Uptake into the storage vesicles is facilitated by active transport by vesicular monoamine transporters (VMAT).

The catecholamines are degraded by two principal enzyme systems, catechol-O-menthyl transferase (COMT) and monamine oxidase (MAO). COMT converts NE and E to their O-methyl metabolites, normetanephrine and metanephrine respectively; after further metabolism these serve as substrates for MAO leading to formation of 3-methoxy 4-hydroxymandelic acid, better known as vanillylmandelic acid (VMA), the major end product of catecholamine metabolism (R).

Catecholamines act through plasma membrane receptors of two broad types, alpha and beta adrenergic receptors (adrenoceptors). Each type includes multiple subtypes (α1, α2, β1, β2, β3, D1); NE and E are mixed agonists. They interact with both alpha and beta adrenergic receptors, although NE has a relatively low affinity for β2 adrenergic receptors including those that mediate vasodilation in skeletal muscles. This probably explains the differences in the hemodynamic responses to E (increased systolic, but not diastolic, blood pressure and increased heart rate) and NE (increased systolic and diastolic blood pressure with reflex restraint of the increase in heart rate).

Clinical presentation

Catecholamine secreting tumors have incidence in male and females in same range and usually occur in middle aged people. In children it is rare, and if it occurs, tends to be multifocal and as a part of genetic syndromes. Classical symptoms are paroxysms which includes sudden onset of headache, sweating, diaphoresis, anxiety and palpitations. It is also associated with labile or sustained hypertension. Typical Spells may be either spontaneous or precipitated by postural change, anxiety, medications (e.g., β-adrenergic antagonists, metoclopramide, anesthetic agents), exercise, or maneuvers that increase intra-abdominal pressure (e.g., change in position, lifting, defecation, exercise, colonoscopy, pregnancy, trauma). Although the types of spells are highly variable but spells tend to be stereotypical for each patient. Frequency of spells are variable.

Signs and Symptoms Associated with Catecholamine-Secreting Tumors [1]

Spell-Related Signs and Symptoms

Anxiety and fear of impending death
Diaphoresis
Dyspnea
Epigastric and chest pain
Headache
Hypertension
Nausea and vomiting
Pallor
Palpitation (forceful heartbeat)
Tremor

Chronic Signs and Symptoms

Anxiety and fear of impending death
Cold hands and feet
Congestive heart failure - dilated or hypertrophic cardiomyopathy
Constipation
Diaphoresis
Dyspnea
Ectopic hormone secretion-dependent symptoms (e.g., CRH/ACTH, GHRH, PTHrP, VIP)
Epigastric and chest pain
Fatigue
Fever
General increase in sweating
Grade II to IV hypertensive retinopathy
Headache
Hyperglycemia
Hypertension
Nausea and vomiting
Orthostatic hypotension
Painless hematuria (associated with urinary bladder paraganglioma)
Pallor
Palpitation (forceful heartbeat)
Tremor
Weight loss

Diagnosis

The diagnosis of pheochromocytoma is based upon clinical suspicion and biochemical confirmation and anatomical localization. Rarely does it happen during investigation for adrenal incidentaloma.

Routine testing for pheochromocytoma in patients with hypertension is both cost-inefficient and unwise - false positive tests would outweigh true positives by a large margin.

Measurement of Fractionated Metanephrines and Catecholamines in Urine and Blood

The diagnosis of catecholamine secreting tumor is established by the presence of increased concentrations of fractionated catecholamines and fractionated metanephrines in urine or plasma. Measurement of fractionated metanephrines and catecholamines in a 24-hour urine collection has high sensitivity, 98%; and specificity, 98%. [2,3] If Measurement of plasma fractionated metanephrines has a sensitivity of 96% to 100%, [3,4] the specificity is poor at 85% to 89%, [3,4,5]. Plasma fractionated metanephrines are useful if used to diagnose pheochromocytoma in high risk patients and in children in whom 24 hour urine collection is difficult.24-hour urinary VMA excretion has poor diagnostic sensitivity and specificity compared with fractionated 24-hour urinary metanephrines. Other tests like estimation of chromogranin and neuropeptide Y lack specificity. Confirmatory tests like clonidine stimulation tests are rarely used.

Localization

Localization studies should not be initiated until biochemical studies have confirmed the diagnosis of a catecholamine-secreting tumor. About 90% of Pheochromocytomas are in the adrenal medullae and 99% are in the abdomen. Most of the remainder are in the mediastinum. Pheochromocytomas are usually localized by computed tomography or magnetic resonance imaging. Although CT is still the primary adrenal imaging modality, MRI has advantages in certain clinical situations.[6]

Imaging characteristics of pheochromocytoma in CT scan are usually large tumors(>3 cms), with smooth margins, and with non homogenous texture and with cystic areas.In MRI it appears hyperintense. Areas of necrosis and calcification are common with pheochromoctoma.

Chemical shift MRI is a form of lipid-sensitive imaging, which helps to differentiate cortical adenoma and pheochromocytoma in difficult situations. If the results of abdominal imaging are negative, scintigraphic localization with 123I-MIBG is indicated. This radiopharmaceutical agent accumulates preferentially in catecholamine-producing tumors; however, this procedure is not as sensitive (sensitivity, 80%; specificity, 99%). [6,7,8]

Normally MIBG is not required in a otherwise diagnosed pheochromocytoma but especially useful in if the adrenal pheochromocytoma is more than 10 cm in diameter or if a paraganglioma is identified on CT or MRI.

Treatment

The treatment of choice for pheochromocytoma is complete surgical resection. Surgical survival rates are 98% to 100% and are highly dependent on the skill of the endocrinologist, endocrine surgeon, and anesthesiologist team. [9,10] Tumor excision usually cures hypertension.

Preoperative preparation of patient is very important as far smooth perioperative course and post operative blood pressure control. Commonest approach is combined and sequential blockade of Alpha & beta adrenergic receptors. Target blood pressure is less than 120/80 mm Hg (seated), with

systolic blood pressure greater than 90 mm Hg (standing). Along with Alpha adrenergic blockade, patients are advised high salt (≥5000 mg/day) for intravascular volume expansion. After adequate α- adrenergic blockade has been achieved, β-adrenergic blockade is initiated, typically 2 to 3 days preoperatively, primarly for control heart rate.

Rate of adrenergic blockade and degree of volume expansion depends upon the patient characteristics. Patients with catecholamine induced vascular changes may require longer period off adrenergic blockade before surgery. Similarly large volume expansion is contraindicated in patients with congestive heart failure or renal insufficiency.

Alpha Blockade is achieved primarily with Phenoxybenazamine, It is an irreversible, long-acting, nonspecific α-adrenergic blocking agent. The initial dosage is 10 mg once or twice daily, and the dose is increased by 10 to 20 mg in divided doses every 2 to 3 days as needed to control blood pressure and spells. Selective α1-adrenergic blocking agents (e.g., prazosin, terazosin, doxazosin) are preferable to phenoxybenzamine in many patients and there is a growing trend of using prazosin for preoperative preparation. Patients to be cautioned regarding orthostatic hypotension and nasal congestion.

Beta adrenergic blockade: Usually done with relatively small doses of short acting betablockers and once tolerates well, change to longacting agents. Titration of dose is done to maintain heart rate less than 80 /minute.

Other Agents: Many patients will require other agents to control the blood pressure apart from Alpha and beta adrenergic antagonists. Major agents used are Calcium channel blockers. Metyrosine (tyrosine hydroxylase inhibitor) is rarely used especially in clinical settings like other drugs are ineffective and in patients whom tumor manipulation is expected.

Follow up

Approximately 1 to 2 weeks after surgery, fractionated catecholamines and metanephrines should be measured by collection of a 24-hour urine specimen and if normal, the resection of the pheochromocytoma should be considered complete. Further Follow up is yearly measurement of Fractionated cathecholamines and metanephrines. If levels are high recurrence is suspected and anatomical diagnosis has to be made.

Genetic syndromes

Genetic syndromes associated with pheochromocytomas are MEN1, MEN 2 A, MEN 2 B, neurofibromatosis type 1, von Hippel Lindau syndrome and familial pheochromocytoma.

Genetic testing

Genetic testing to be carried out in patients with family history of pheochromocytoma; paraganglioma; and any sign that suggests a genetic cause, such as retinal angiomas, axillary freckling, cafe au lait spots, cerebellar tumor, MTC, or hyperparathyroidism. In addition, all first-degree relatives of a patient with pheochromocytoma or paraganglioma should have biochemical testing.

Paraganglionomas

Cathecholamine secreting tumors originating from sympathetic ganglia are known as paragnagliomas. Clinically and biochemically they are similar to pheochromocytomas. These

tumors are suspected after confirming high catecholamine levels and adrenals are found normal in imaging . Major genetic syndrome associated with paragangliomas is SDH mutations (succinate dehydrogenase) This is subdivided to SDH B, SDH C & SDH D types.

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