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PHEOCHROMOCYTOMA IN PEDIATRICS

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ABSTRACT

Pheochromocytomas are rare tumors originating in the adrenal medulla. They may be sporadic or in the context of a hereditary syndrome. A considerable number of pheochromocytomas carry germline or somatic gene mutations, which are inherited in the autosomal dominant way. All patients should undergo genetic testing. Symptoms are due to catecholamines over production or to a mass effect. Diagnosis is confirmed by raised plasma or urine metanephrines or normetanephrines. Radiology assists in the tumor location and any local invasion or metastasis. All the patients should have preoperative preparation with α-blockers and/or other medications to control hypertension, arrhythmia, and volume expansion. Surgery is the definitive treatment. Follow up should be life-long.

KEYWORDS: Epidemiology; genetics; medication; pathology; pheochromocytoma; radiology; surgery; symptoms; treatment.

1) INTRODUCTION

Pheochromocytoma is a condition due to a Catecholamine-secreting tumor formed by chromaffin cells within the adrenal gland. These tumors may arise sporadically or may be inherited as features of multiple endocrine neoplasia type 2 (MEN-2), von Hippel-Lindau (VHL) disease or several other pheochromocytoma associated syndromes. These are well vascularized tumors. The name pheochromocytoma reflects the formerly used black-colored staining caused by chromaffin oxidation of catecholamines.

2) LAYERS OF THE ADRENAL GLAND

The cortex of the suprarenal gland is comprised of three distinct morphological zones, the zona glomerulosa, zona fasciculata, and the zona reticularis. These lie above the medulla of the suprarenal gland.

A) ZONA GLOMERULOSA

The zona glomerulosa is the outer zone of the cortex and comprises nearly 10% of the cortical mass. It consists of a thin area of small, polyhedral cells which are clumped together in groups. Inside each cell, prominent organelles include a large amount of smooth endoplasmic reticulum present in the basophilic cytoplasm, as well as a small number of lipid droplets. These store cholesterol, the main precursor of steroid biosynthesis. These are important organelles as they relate to the cell's primary function. In particular, the zona glomerulosa secretes mineralocorticoids such as aldosterone, a component of the renin-angiotensin-aldosterone-system (RAAS). These play a crucial role in maintaining blood pressure, blood volume, and electrolyte homeostasis.

B) ZONA FASCICULATA

The zona fasciculata is made of cells which are large and polyhedral. These are aligned together to form linear columns, which run the depth of the zona fasciculata. Long sinusoids from the capsular plexus travel alongside these cellular columns, supplying the cortex throughout. The sinusoidal paths end as they come together in the zona reticularis to form a vascular network.

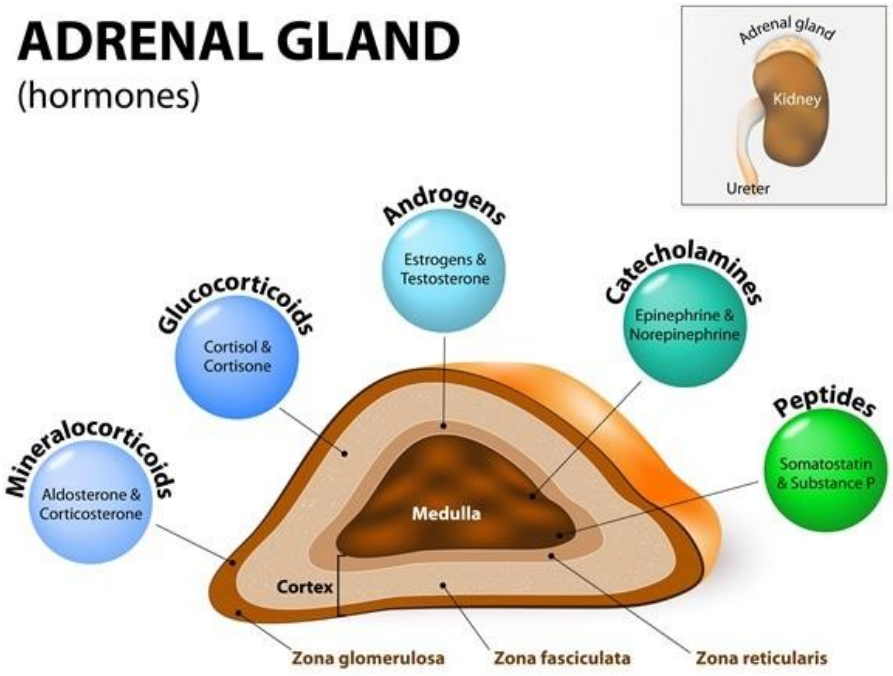
Inside the cells of the zona fasciculata, prominent organelles include a large amount of smooth endoplasmic reticulum present in the basophilic cytoplasm, as well as a large number of lipid droplets. These store cholesterol, the main precursor of steroid biosynthesis. These are important organelles as they relate to the cell's primary function. In particular, the zona fasciculata secretes glucocorticoids, such as cortisol. These glucocorticoids are involved in, anti-inflammatory and immunosuppressive processes. They also have a physiological role in the metabolism of carbohydrates and proteins.

C) ZONA RETICULARIS

The zona reticularis is the innermost section of the suprarenal cortex. Unlike the other cortical regions, it does not differentiate completely until childhood.

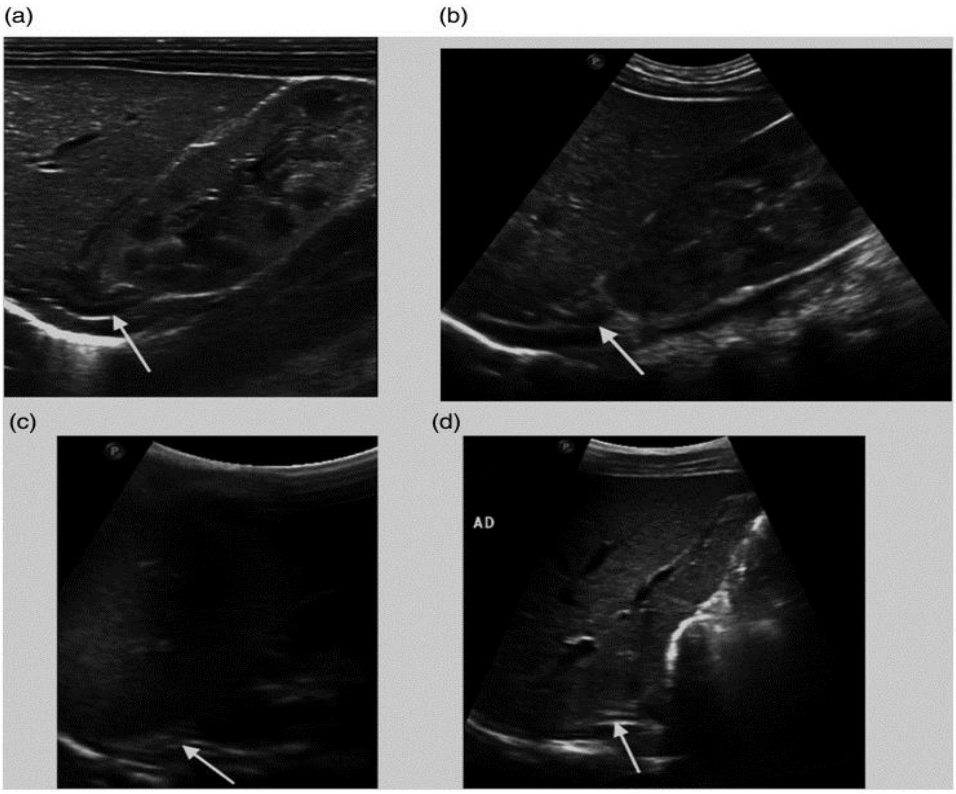
The zona reticularis is made of a network of cellular pillars interconnected with each other. The cells of this region contain numerous lysosomes to generate a cholesterol-rich supply. This lysosomal digestion process results in speckles of yellow-brown pigments within the cell. In particular, the zona reticularis secretes androgens, such as dehydroepiandrosterone (DHEA), its sulfated form DHEAS, and androstenedione. These are prohormones which must be converted to sex hormones in the gonads. In females, they are thought to contribute to the development of secondary sexual characteristics.

- **MEDULLA**
  - The adrenal (suprarenal) medulla, or the medulla of the suprarenal gland, refers to the inner central part of each adrenal gland and is derived from neural crest cells. It is a thin region and forms approximately one-tenth of the gland. The adrenal medulla is nearly completely surrounded by the yellowish cortex, with the exception of the hilum which transmits the neurovasculature of the gland. The adrenal medulla is extensively vascularized, and depending on the amount of blood within it, the adrenal medulla may appear as either dark red, brownish or greyish.
  - Histologically, the adrenal medulla consists of clusters and columns of large spherical chromaffin cells, also called pheochromocytes, between which run capillaries and sinusoids, within a supporting network of reticular fibres. The chromaffin cells are regarded as modified ganglionic cells of the sympathetic nervous system since they are derivatives of neural crest cells.
  - Functionally, the chromaffin cells are similar to postganglionic sympathetic neurons. They synthesize and store the catecholamine hormones noradrenaline (norepinephrine) and adrenaline (epinephrine) in granules. Preganglionic sympathetic nerve fibers within the adrenal medlla form synapses with the chromaffin cells. In response to signals from these preganglionic neurons, the chromaffin cells release the hormones, mainly adrenalin, from their granules into the venous sinusoids and ultimately into circulation via the central medullary vein and hilar suprarenal vein to affect target cells.
  - The hormones noradrenaline and adrenaline stimulate a flight-or-fight response that prepares the body for an emergency defensive reaction. Specifically, these hormones result in various target organ effects including an elevated heart rate and blood pressure, bronchodilation, increased blood glucose and redistribution of blood flow to vital organs.



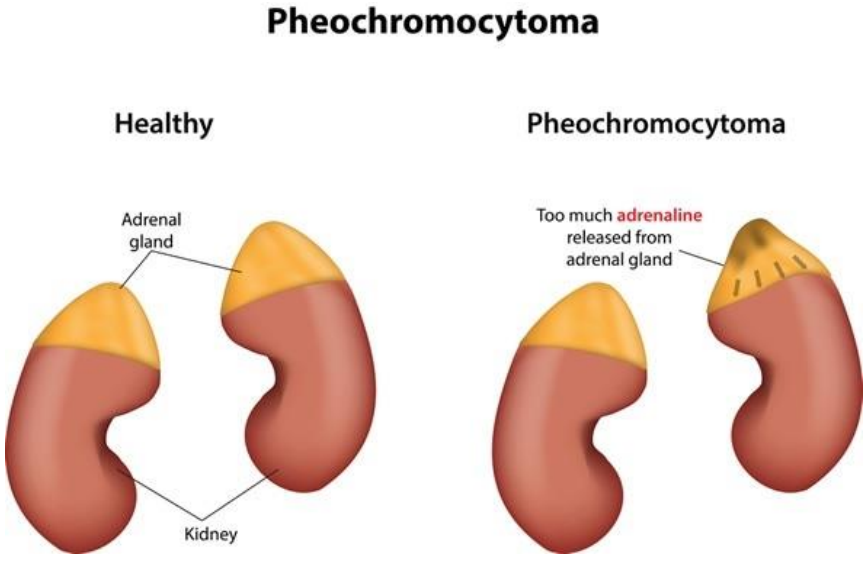
ADRENAL GLANDS IN PEDIATRICS

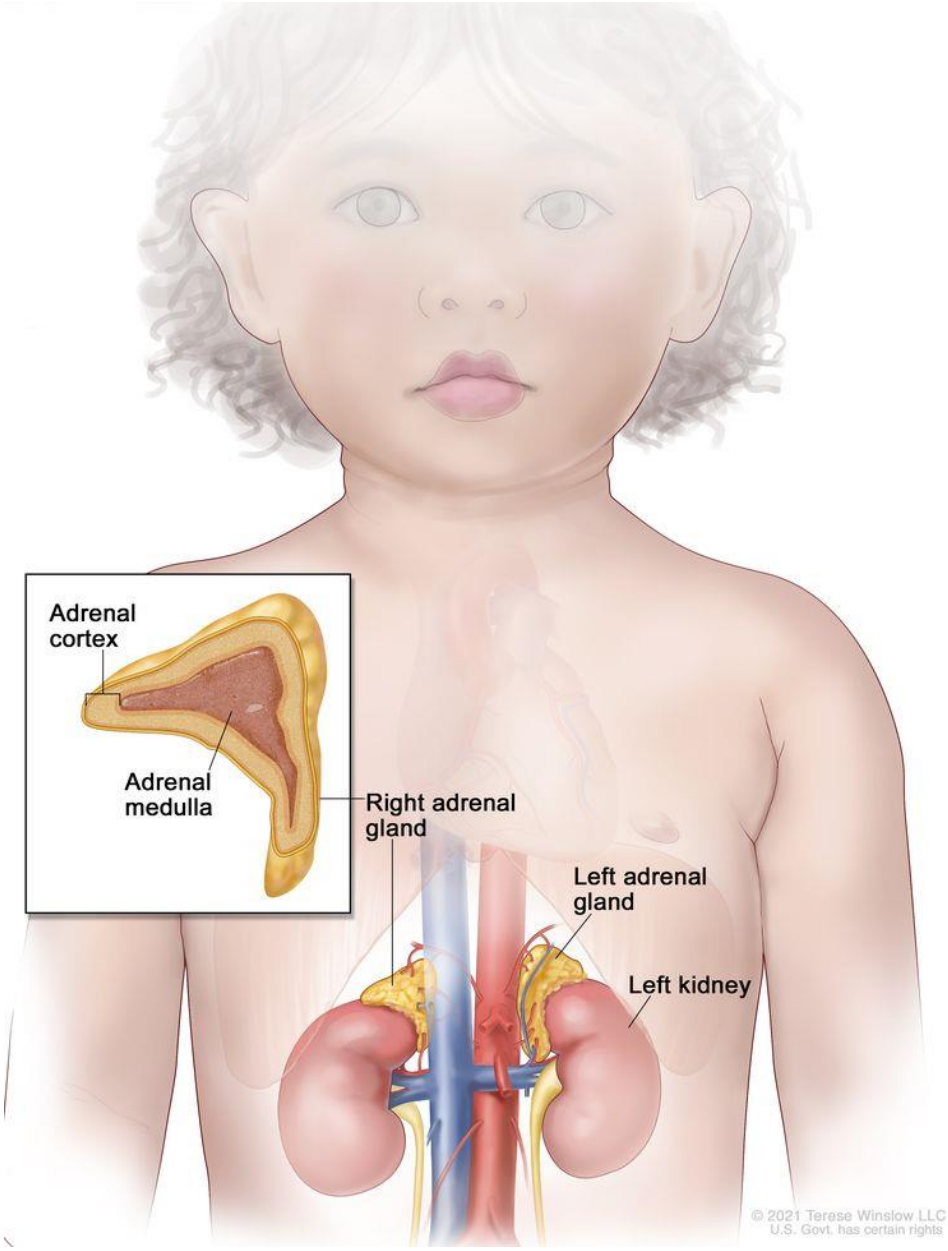
At birth the adrenal gland is relatively large at one-third of the size of the kidney. This reduces to one-thirtieth of the size of the kidney in the adult. However, the mass of an adrenal gland is similar at birth compared to adulthood; it weighs about 5 g. The gland atrophies after birth and serial sonographic examinations have shown a decrease in size of up to 50% in the first six weeks postnatally. From the second year of life it slowly grows and reaches adult size at puberty(Figure). It is possible to measure the gland on ultrasound with the normal neonatal adrenal length described as between 0.9 and 3.6 cm (mean 1.5–1.7 cm) and limb thickness between 0.2 and 0.5 cm (mean 0.3 cm). In older children and adults, the adrenal gland measures 4–6 cm in length with 0.2–0.6 cm in limb thickness.



Normal right adrenal gland at different ages. Longitudinal section of the right adrenal gland (arrow) in (a) a neonate, (b) in a six-week-old child, (c) at three years of age, and (d) eight years of age. Later in life the adrenal gland appears hypoechoic with surrounding hyperechoic fat.

Although there can be considerable variation, the right adrenal gland is usually triangular or pyramidal in shape, whilst the left is normally semilunar.[3] When viewed in longitudinal section, the adrenals adopt an inverted V or Y shape, and in transverse section they appear as L, V, or Y shaped. The ultrasound appearances of the normal adrenal gland change with age. The gland consists of a central hyperechoic medullary layer; this develops from neuroendocrine tissue and is responsible for the production of catecholamines. The cortex arises from coelomic mesoderm and is hypoechoic. In the neonate the large hypoechoic cortex comprises a thick transient inner foetal zone that atrophies over time, and a thin outer zone, that becomes the permanent adult cortex. The cortex differentiates into three zones and secretes aldosterone, glucocorticoids, and androgens. At approximately 5–6 months, the entire gland can appear hyperechoic as most of the hypoechoic foetal zone has atrophied, replaced by fibrous tissue. As the fibrous tissue regresses the gland becomes hypoechoic in appearance, and after one year of age it resembles the hypoechoic adult gland surrounded by hyperechoic fat.





3) PATHOGENESIS

Catecholamines are produced in the chromaffin cells starting with the rate-limiting step of tyrosine hydroxylase (TH), regulating the conversion of tyrosine to dihydroxyphenylalanine (DOPA). Di-hydroxyphenylalanine is subsequently converted into dopamine by the action of dopa decarboxylase, which is further converted into norepinephrine by the action of dopamine β-hydroxylase. PNMT(phenylethanolamine-N-methyltransferase) enzyme methylates the norepinephrine to epinephrine. These catecholamines are sequestered in storage vesicles and released into circulation, and cardiac manifestations are mediated through the adrenoreceptors.

Pheochromocytomas release these catecholamines in various patterns ranging from paroxysmal, continuous, and mixed patterns. Norepinephrine is released continuously and can result in persistent hypertension, while epinephrine is released in a paroxysmal pattern resulting in tachyarrhythmias. Alpha(1,2) and beta(1,2) adrenoreceptors bind epinephrine and norepinephrine with varying affinities. These adrenoceptors are influenced by glucocorticoids and thyroid hormones and can result in either an increased number of adrenoceptors or affect their affinity.

The heart has Beta-1 adrenoceptors, and stimulation of these receptors leads to the activation of adenylate cyclase through the guanine triphosphate protein-coupled receptor(Gs). Activating adenylate cyclase (AC) can convert adenosine triphosphate to cyclic adenosine monophosphate (cAMP). This results in the activation of hyperpolarization-activated cyclic nucleotide-gated(HCN) channels and protein kinase (PKA). This cascade of activities can result in increased ionotropy in SA nodal cells and increased dromotropy in AV nodal cells.

Ryanodine-2 receptors (RyR2) present on the sarcoplasmic reticulum of cardiac myocytes are also phosphorylated by protein kinase A and cause calcium efflux into the cytosol. Calcium binding to the troponin-tropomyosin complex escalates cross-bridge cycling and inotropy by revealing myosin binding sites on actin.

Beta-2 adrenoceptors are present in the peripheral blood vessels and can cause vaso-dilation when activated by epinephrine and norepinephrine. Alpha(1)-adrenoreceptors are present in the vascular smooth muscle cells and can lead to hypertension induced by vasoconstriction after being activated by norepinephrine and epinephrine. Synaptic nerve terminals have Alpha-2 adrenoceptors which inhibit the release of norepinephrine.

4) CLINICAL MANIFESTATIONS

Classically, pheochromocytoma manifests as spells with the following 4 characteristics

- Headaches
- Palpitations
- Diaphoresis
- Severe hypertension

Typical patterns of the spells are as follows

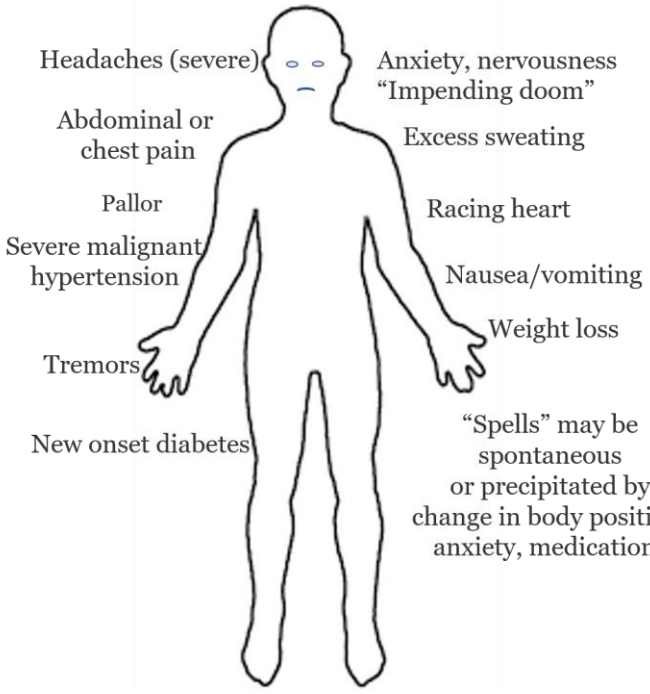
- Frequency may vary from monthly to several times per day
- Duration may vary from seconds to hours
- Over time, spells tend to occur more frequently and become more severe as the tumor grows

The following may also occur during spells

- Tremor
- Nausea
- Weakness
- Anxiety, sense of doom
- Epigastric pain
- Flank pain
- Constipation

Clinical signs associated with pheochromocytomas include the following

- Hypertension: Paroxysmal in 50% of cases
- Postural hypotension: From volume contraction
- Hypertensive retinopathy
- Weight loss
- Pallor
- Fever
- Tremor
- Neurofibromas
- Tachyarrhythmias
- Pulmonary edema
- Cardiomyopathy
- Ileus
- Café au lait spots



5) DIAGNOSIS

Establishing the diagnosis of pheochromocytoma is dependent on the demonstration of significant catecholamine excess. Levels of epinephrine (adrenaline), norepinephrine (noradrenaline), and their metabolites (breakdown products of epinephrine and norepinephrine) can be measured in either urine or blood. Catecholamine metabolites include metanephrine, normetanephrine, dopamine, and vanillylmandelic acid (VMA). Because catecholamine relase varies throughout the day, the best method of diagnosing pheochromocytomas is using a 24-hour urine collection.

This involves obtaining a special urine container, which has a small amount of preservative, from a medical laboratory and filling it with one entire day's worth of urine. The test is somewhat inconvenient but well worth the trouble due to its reliability and unrivaled specificity. Frequently, the 24-hour urine collection must be performed more than once to establish diagnostic certainty.

A 24-hour urine test for pheochromocytoma is considered positive if the catecholamine levels exceed two times the upper limit of normal. Many people, particularly those with hypertension, have mildly elevated catecholamine levels that are technically above what is considered the normal range, but fall below two times the upper limit. Virtually none of these people with mild catecholamine excess will turn out to have pheochromocytomas in the final analysis.

Blood tests are available for metanephrine, normetanephrine, and chromogranin A. The most commonly ordered blood test for pheochromocytoma is the plasma free metanephrine test. Though more convenient to obtain than a 24-hour urine collection, plasma free metanephrine testing is plagued by frequent false positive results. In other words, the tests creates a false alarm where the patient appears to have a pheochromocytoma, but in reality s/he does not. False positive results like these are a frequent source of confusion for both patients and physicians alike. For this reason, 24-hour urine testing remains the gold standard.

Imaging tests and scans Imaging should only be performed after the diagnosis of pheochromocytoma has been established with 24-hour urine testing. Several types of scans can be used to locate pheochromocytomas. These include cross-sectional scans, functional scans, and co-registered (hybrid cross-sectional and functional) scans. Cross-sectional scans yield detailed anatomic information, whereas functional scans utilize specific molecules (tagged with tiny amounts of a radioactive tracer) that target specific tumor properties.

Cross-sectional scans
Computed tomography (CT or CAT scan)
Magnetic resonance imaging (MRI)
Functional scans
131I-meta-iodobenzylguanidine scintigraphy (MIBG scan)
18F-deoxyglucose positron emission tomography (regular PET scan, also known as FDG-PET scan)
Co-registered scans
FDG-PET/CT scan
18F-DOPA PET/CT scan

DIFFERENTIAL DIAGNOSIS

- **Pheochromocytoma Vs Paragangloma**

Pheochromocytoma and paraganglioma are rare tumors that come from the same type of tissue. Pheochromocytoma is a rare tumor that forms in the adrenal medulla (the center of the adrenal gland). Paragangliomas form outside the adrenal gland. Some inherited disorders and changes in certain genes increase the risk of pheochromocytoma or paraganglioma. Signs and symptoms of pheochromocytoma and paraganglioma include high blood pressure and headache. Signs and symptoms of pheochromocytoma and paraganglioma may occur at any time or be brought on by certain events. Tests that examine the blood and urine are used to diagnose pheochromocytoma and paraganglioma. Genetic counseling is part of the treatment plan for patients with pheochromocytoma or paraganglioma. Certain factors affect prognosis (chance of recovery) and treatment options.

- **Pheochromocytoma Vs Adrenal Carcinoma**

Adrenocortical carcinoma (ACC) is a malignant tumour arising from the adrenal cortex, whereas pheochromocytoma is a tumour of the adrenal medulla with occasional presence at extra-adrenal sites. Most of the adrenocortical tumours present clinically with Cushing's syndrome and signs of virilization due to over-production of the respective hormones. It is, however, rare for an adrenocortical tumour to present clinically as a pheochromocytoma. We report the case of a 45-year-old female presenting with clinical symptoms and signs of pheochromocytoma and investigations that resulted in a diagnostic dilemma. The histopathological examination confirmed the presence of ACC after the tumour was excised. This phenomenon was due to the presence of neuroendocrine features of ACC referred to, as a pseudo-pheochromocytoma with extremely limited data in the literature.

- **Pheochromocytoma As An Etiology of Cushing's Syndrome**

Pheochromocytomas are rare catecholamine-secreting tumors of the adrenal medulla that may also secrete ACTH. There are approximately 100 cases of ACTH-producing pheochromocytomas reported in the peer reviewed literature, and they typically cause Cushing syndrome by significantly raising circulating ACTH levels. We report a pheochromocytoma causing apparent ACTH-independent Cushing syndrome by paracrine action of locally produced ACTH on ipsilateral adrenal cortex. **Case:** A 64-year-old female was referred for an incidentally discovered left adrenal mass. The mass was 4 cm and 37 Hounsfield units on non-contrast computed tomography, and the right adrenal gland was unremarkable. The patient's history was notable for three years of resistant hypertension, and examination revealed stigmata of Cushing syndrome including moon facies, scattered bruises, and wide, pink striae. Three measurements of plasma metanephrines ranged from 3- to 4.5-fold elevated, and 24 h urine metanephrines were 5.2-fold elevated. Urine 24 h epinephrine was 2.7-fold elevated. Three 8 AM cortisol measurements on overnight dexamethasone suppression tests were 16.3–17.4 mcg/dL (< 1.8), and 8 AM dexamethasone on one test was 494 ng/dL (140–295). Two midnight salivary

cortisol measurements were 0.348 and 0.416 mcg/dL (< 0.112), and 8 AM ACTH levels on two occasions were 6.8 and 7.9 pg/mL (7.2–63.3). After adrenergic blockade, the patient underwent left adrenalectomy. Her tumor stained for synaptophysin and chromogranin consistent with pheochromocytoma, and focal staining for ACTH was also observed. Hyperplasia of the adjacent adrenal cortex was present. Hypertension resolved after adrenalectomy, and the patient developed secondary adrenal insufficiency (8 AM cortisol and ACTH 1.0 mcg/dL [> 15] and 2.9pg/mL, respectively).

DISCUSSION

There are five published reports of pheochromocytoma and subclinical hypercortisolemia due to paracrine ACTH or IL-6 activity on ipsilateral adrenal cortex, but this case is distinguished by the occurrence of overt Cushing syndrome. Our patient had ACTH < 10 pg/mL on two measurements, her pheochromocytoma showed focal staining for ACTH, and hyperplasia of adjacent adrenal cortex was observed. In contrast, median ACTH level was 5-6x above the upper limit of normal in a recent review of 95 cases of pheochromocytomas with Cushing syndrome due to ectopic ACTH secretion. If Cushing syndrome was due to bilateral adrenal hyperplasia independent of the patient's pheochromocytoma, cortisol excess would not have resolved after unilateral adrenalectomy. Communication between cortical and medullary circulations through venous radicles provides a mechanism for ACTH produced by the patient's pheochromocytoma to affect the function of adjacent cortex. This case demonstrates a novel mechanism by which ACTH from a pheochromocytoma can cause Cushing syndrome.

- **PHEOCHROMOCYTOMA AND ADDISON'S DISEASE**

Addison's disease is a condition characterized by the insufficient production of adrenal hormones, including cortisol and aldosterone. In some cases, pheochromocytoma can coexist with autoimmune adrenalitis, which is the main cause of Addison's disease. Autoantibodies against 21-hydroxylase, an enzyme involved in cortisol production, are present in both conditions. Therefore, the presence of pheochromocytoma may indicate an increased risk of developing Addison's disease in individuals with autoimmune adrenalitis. However, further research is needed to fully understand the relationship between these two conditions.

- **CONGENITAL ADRENAL HYPERPLASIA**

Congenital adrenal hyperplasia (CAH) is a genetic disorder in which the two adrenal glands (located at the top of the kidneys) do not function properly. CAH is caused by genetic defects in the proteins and enzymes involved in cortisol biosynthesis. The most common mutation is in the gene encoding the adrenal steroid 21-hydroxylase, which is an enzyme responsible for converting cholesterol to **cortisol** within the adrenal glands. Without this enzyme, the adrenal glands may produce too little cortisol and/or aldosterone and too much androgen.

Classic CAH is usually diagnosed in infancy or early childhood and is the most severe, life- threatening type. In one form of classic CAH, called "salt-wasting" (meaning the body has trouble keeping the right amount of salt in the blood), the adrenal glands do not make enough cortisol and aldosterone. If not found and treated, classic CAH can cause shock, coma, and death.

Nonclassic CAH is a more common, less severe condition in which there is still some adrenal steroid 21-hydroxylase enzyme activity remaining. It is usually diagnosed in later childhood or adulthood. Nonclassic CAH does not cause "salt-wasting." Symptoms of nonclassic CAH include early puberty in children and irregular menstrual periods, acne, and/or unwanted hair growth in women.

6) TREATMENT

Four types of standard treatment are used

Surgery to remove the tumor is the main treatment for pheochromocytoma and paraganglioma. For several days before surgery, your child may need to take blood pressure medicine to lower the risk of complications during and after surgery.

Chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy).

131I-MIBG therapy is a treatment with high-dose radioactive iodine. The radioactive iodine is given through an intravenous (IV) line and enters the bloodstream which carries radiation directly to tumor cells. Radioactive iodine collects in pheochromocytoma and paraganglioma cells and kills them with the radiation that is given off.

Targeted therapy is a type of treatment that uses drugs or other substances to identify and attack specific cancer cells. Targeted therapies usually cause less harm to normal cells than chemotherapy or radiation therapy do.

7) REFERENCES

1. https://pubmed.ncbi.nlm.nih.gov/31517632/
2. https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/rare-endocrine-tumor/pheochromocytoma#:~:text=Pheochromocytoma%20is%20a%20type%20of,on%20top%20of%20the%20kidneys.
3. https://www.nhs.uk/conditions/phaeochromocytoma/
4. https://www.hopkinsmedicine.org/health/conditions-and-diseases/adrenal-tumors--pheochromocytoma

5. https://www.urologyhealth.org/urology-a-z/p/pheochromocytoma-(adrenal-medulla-tumor)
6. https://rarediseases.org/rare-diseases/pheochromocytoma/
7. https://www.sciencedirect.com/topics/medicine-and-dentistry/pheochromocytoma
8. https://www.sciencedirect.com/topics/medicine-and-dentistry/pheochromocytoma
9. https://emedicine.medscape.com/article/988683-overview?form=fpf
10. https://www.britannica.com/science/pheochromocytoma
11. https://www.stanfordchildrens.org/en/topic/default?id=pheochromocytoma-in-children-90-P01971
12. https://academic.oup.com/jcem/article/99/6/1915/2537399