Supportive module 1: "Essentials of diagnosis, treatment and prevention of major endocrine diseases"			
4.	Diseases of the adrenal glands. Chronic adrenal insufficiency. Hormonally active tumors.	2	27/09
5.	Diseases of the hypothalamic-pituitary system. Its part in correction of the functional activity of the endocrine glands.	2	04/10

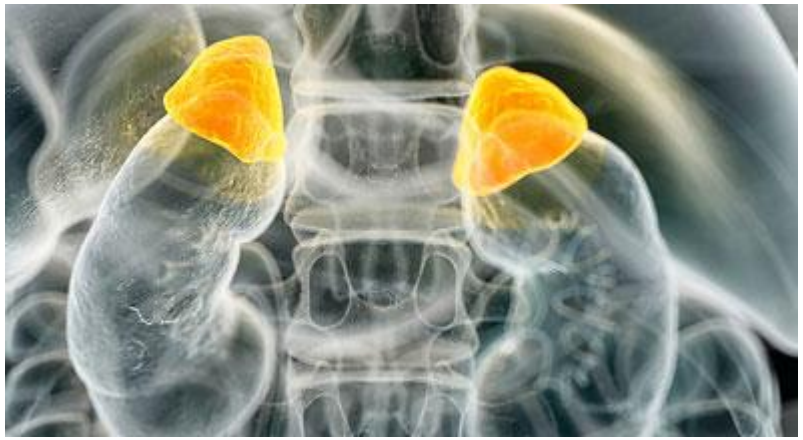
Essentials of Diagnosis, Treatment and Prevention of Major Endocrine Diseases:

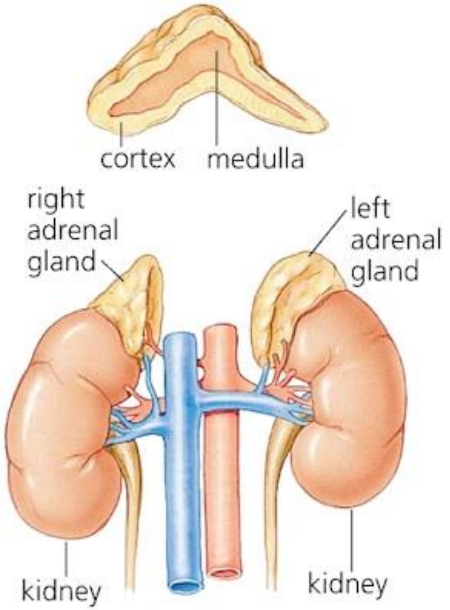
Diseases of the Adrenal Glands. Adrenal Insufficiency. Adrenal Hyperfunction. Hormonally Active Tumors.

LECTURE IN INTERNAL MEDICINE FOR IV COURSE STUDENTS

M. Yabluchansky, L. Bogun, L. Martymianova, O. Bychkova, N. Lysenko, N. Makienko
V.N. Karazin National University Medical School' Internal Medicine Dept.

Plan of the Lecture





- Definition
- Epidemiology
- Risk factors
- Etiology
- Mechanisms
- Classification
- Clinical presentation
- Diagnosis
- Treatment
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic guidelines

http://www.thelancet.com/pb/assets/raw/pb/assets/raw/Lancet/clinical/diseases/Cushing's.jpg http://peninsulamassage.com.au/wp-content/uploads/2012/08/Adrenal_Glands_1.jpg

Definition

Diseases of the Adrenal Glands

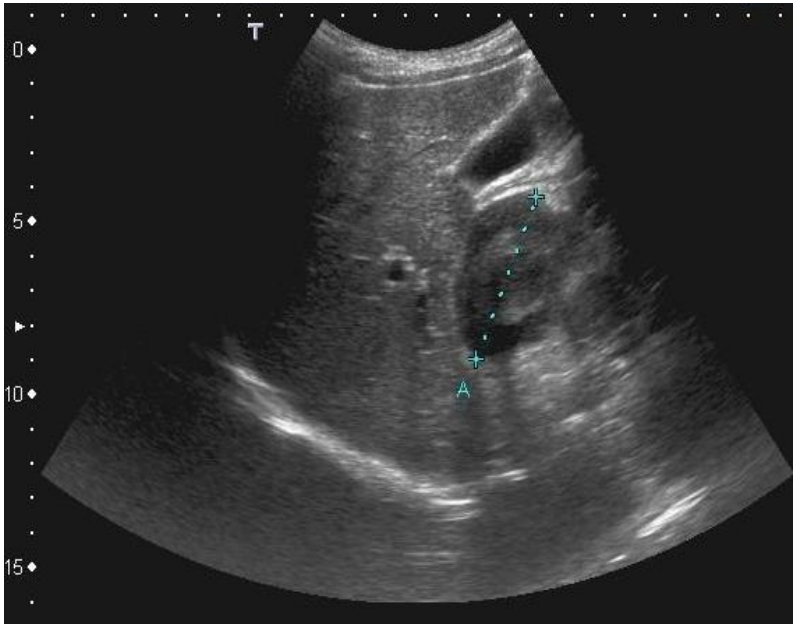
- Diseases of the Adrenal Glands are conditions that interfere with the normal functioning of the adrenal glands and may cause hyperfunction (Overactive Adrenal Glands) or hypofunction (Underactive Adrenal Glands), and may be congenital or acquired.
- There are two parts of the adrenal glands, the cortex, derived from mesenchymal cells, and the medulla, derived from neuroectodermal cells; first one produces mineralocorticoids, glucocorticoids, and androgens; and second one produces epinephrine (adrenaline) and norepinephrine(noradrenaline).

https://en.wikipedia.org/wiki/Adrenal_gland_disorder

Epidemiology

Epidemiologic study of adrenal gland disorders in Japan

- The total numbers of patients in Japan in 1997 were estimated as 1,450 for primary aldosteronism, 1,250 for Cushing's syndrome, 290 for adrenal preclinical Cushing's syndrome, 660 for Addison's disease, and 1,030 for pheochromocytoma
- For the first time, a reliable national estimation of the prevalence of disorders of adrenal hormones was conducted in this study



Abdominal ultrasonography revealed a 5cm heterogeneous nodule in the right adrenal gland

http://www.eurorad.org/eurorad/view_figure.php?pubid=11230&figid=34889&nr=1&lang=en http://www.ncbi.nlm.nih.gov/pubmed/10915016

Risk Factors

- There does not appear to be a particular group who is most at risk for adrenal gland disorders
- While there are certain risk factors for adrenal gland disorders, most of them occur without apparent cause, where risk factors are absent
- The risk of development adrenal diseases may be increased by genetic predisposition; by a problem in another gland, such as the pituitary gland, or when a disease or infection affects one or both of the adrenal glands; and certain lifestyle behaviors and environmental factors, such as smoking and exposure to carcinogens
- Adrenal gland disorders appear to affect men, women, and children equally and may develop at any age.

http://www.cancercenter.com/adrenal-cancer/risk-factors/ sharecare.com/health/adrenal-gland/who-risk-adrenal-gland-disorders

Etiology

- Congenital anomalies (genetic mutations)
- Immunopathology
- Infections (e.g., tuberculosis, acquired immune deficiency syndrome (AIDS))
- A problem in another glands, such as the pituitary, which regulate the adrenal gland
- Tumors including pheochromocytomas
- Bilateral adrenal hemorrhage or infarction
- Bilateral adrenalectomy
- Certain medicines

https://medlineplus.gov/adrenalglanddisorders.html

Mechanisms

- The major disorders of the adrenal cortex are characterized by excessive or deficient secretion of each type of adrenocortical hormone accordingly to interference of etiologic and pathogenetic factors that include distress, injury, vascular reactions, thrombosis, necrosis, acute and chronic inflammation, dystrophy, hypertrophy, neoplastic processes, etc.
- The most common disorder of the adrenal medulla is pheochromocytoma, that originates from chromaffin cells and excretes catecholamines, but pheochromocytoma may be referred to as secreting paragangliomas when found in extra-adrenal chromaffin cells; neoplasms, such as neuroblastomas and ganglioneuromas, may also be of neuronal lineage.

http://accessmedicine.mhmedical.com/content.aspx?bookid=339&sectionid=42811321 ncbi.nlm.nih.gov/pmc/articles/PMC2576282/

International Classification of Diseases

Chapter IV
(E00-E90) Endocrine, nutritional and metabolic diseases

(E20-E35) Disorders of other endocrine glands

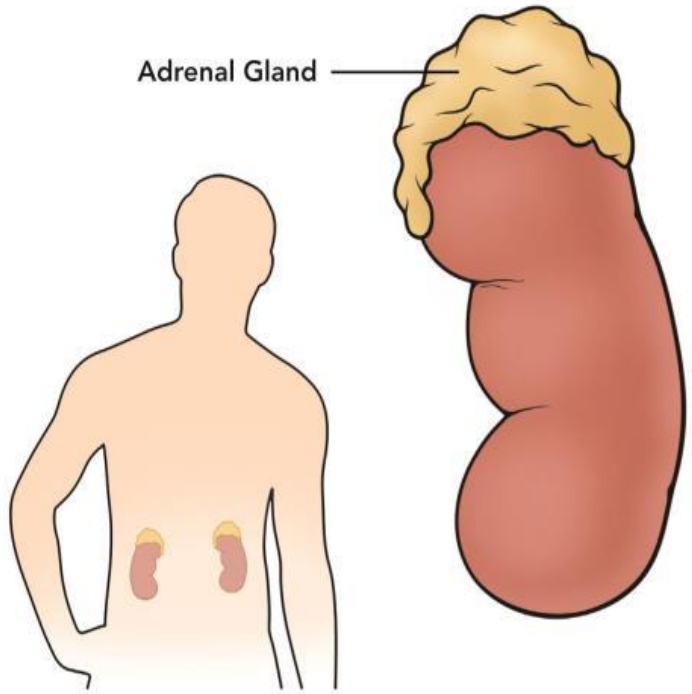
E26 Hyperaldosteronism: E26.0 Primary hyperaldosteronism, E26.1 Secondary hyperaldosteronism, E26.8 Other hyperaldosteronism (Bartter syndrome), E26.9 Hyperaldosteronism, unspecified

E27 Other disorders of adrenal gland: E27.0 Other adrenocortical overactivity, E27.1 Primary adrenocortical insufficiency, E27.2 Addisonian crisis, E27.3 Drug-induced adrenocortical insufficiency, E27.4 Other and unspecified adrenocortical insufficiency, E27.5 Adrenomedullary hyperfunction, E27.8 Other specified disorders of adrenal gland, E27.9 Disorder of adrenal gland, unspecified

http://apps.who.int/classifications/icd10/browse/2016/en#/E00-E07

Clinical classification

- Adrenal Insufficiency (AI)
- Adrenal Hyperfunction (AH)
- Primary Hyperaldosteronism
- Glucocorticoid-Remediable Hyperaldosteronism
- Pheochromocytoma
- Adrenal Hyperandrogenism
- Nonclassic Congenital Adrenal Hyperplasia
- Androgen-Secreting Adrenal Tumors
- Adrenal Incidentaloma
- Considerations of the Pharmacologic use of Glucocorticoids



http://www.hormone.org/ clevelandclinicmeded.com/medicalpubs/diseasemanagement/endocrinology/diseases-of-the-adrenal-gland/

Adrenal Insufficiency

Etiology of Primary Adrenal Insufficiency

- The most common cause of primary adrenal insufficiency (AI) is autoimmune destruction of the adrenal glands (Addison's disease - 70%-90% of all causes
- Some other causes of primary AI include bilateral adrenal hemorrhage, drugs (e.g., mitotane, etomidate, ketoconazole), infectious diseases (e.g., tuberculosis, HIV infection, disseminated histoplasmosis, paracoccidiomycosis)) affects glucocorticoid and mineralocorticoid secretion and may be fatal if untreated
- Addison's disease may coexist with other autoimmune conditions, such as type 1 diabetes, hypothyroidism, or hypoparathyroidism.

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Adrenal Insufficiency

Etiology of Secondary and Tertiary Adrenal Insufficiency

- Secondary and tertiary AI occur commonly after the discontinuation of glucocorticoids
- Less frequently, adrenocorticotropic hormone (ACTH) deficiency may be caused by pituitary macroadenomas, pituitary surgery or radiation, and parasellar diseases
- Megestrol acetate, an appetite stimulator used in some patients with advanced cancer or cachexia related to AIDS may be associated with secondary AI
- Tertiary AI results from the inadequate secretion of corticotropin-releasing hormone (CRH0
- Secondary and tertiary AI only affect cortisol secretion, because ACTH has only a minor role in regulation of aldosterone secretion.

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Adrenal Insufficiency

Manifestations

- All patients with primary AI complain of fatigue, anorexia, and weight loss; skin hyperpigmentation, initially on the extensor surfaces, palmar creases, and buccal mucosa, results from increased levels of ACTH and other pro-opiomelanocortin–related peptides, including melanocyte-stimulating hormone
- Secondary AI manifests more insidiously with lack of skin hyperpigmentation, salt craving, metabolic acidosis, and hyperkalemia, because mineralocorticoid secretion is intact; fatigue, hyponatremia, and hypoglycemia are some of the clinical manifestations in secondary adrenal insufficiency.

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Adrenal Insufficiency

Symptoms, Signs and Laboratory Abnormalities

Symptoms

- Weakness, fatigue
- Anorexia
- Nausea
- Vomiting
- Constipation
- Diarrhea
- Abdominal pain
- Salt craving
- Postural dizziness
- Muscle and joint pain

Signs

- Weight loss
- Hyperpigmentation
- Vitiligo
- Systolic blood pressure <110 mm Hg

Laboratory Abnormalities

- Hyponatremia
- Hyperkalemia
- Hypercalcemia
- Azotemia
- Anemia
- Eosinophilia

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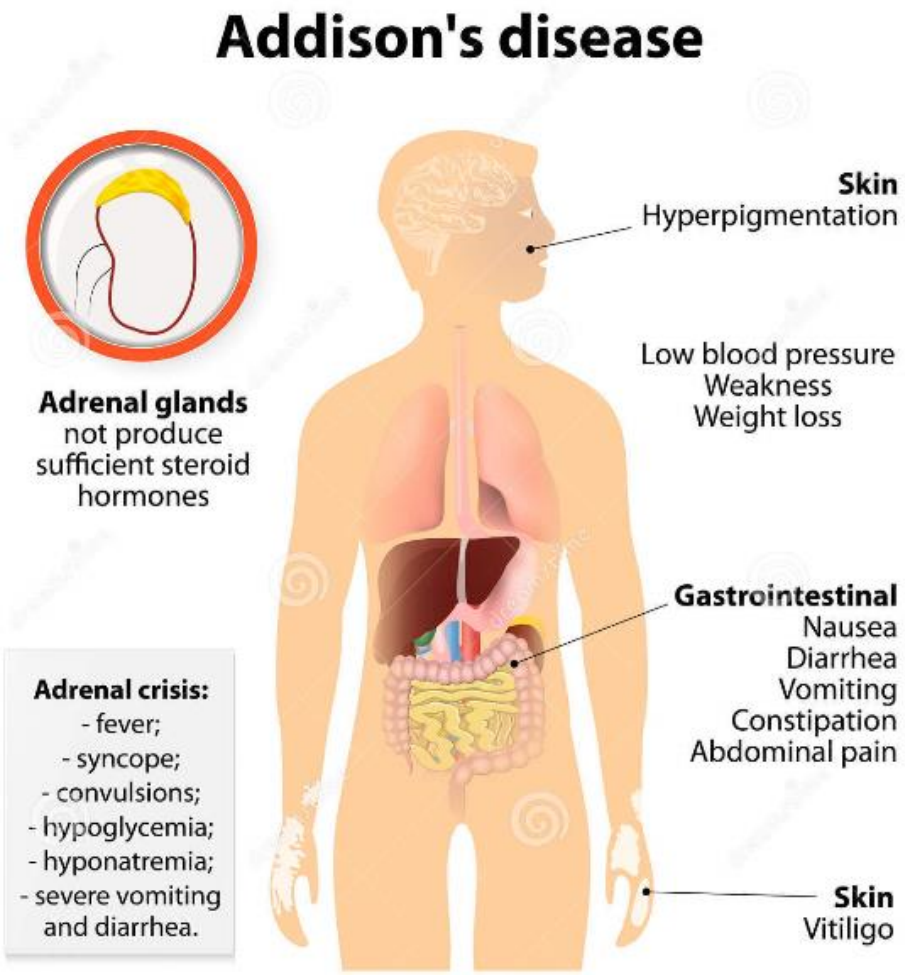
Adrenal Insufficiency

Symptoms, Signs and Laboratory Abnormalities



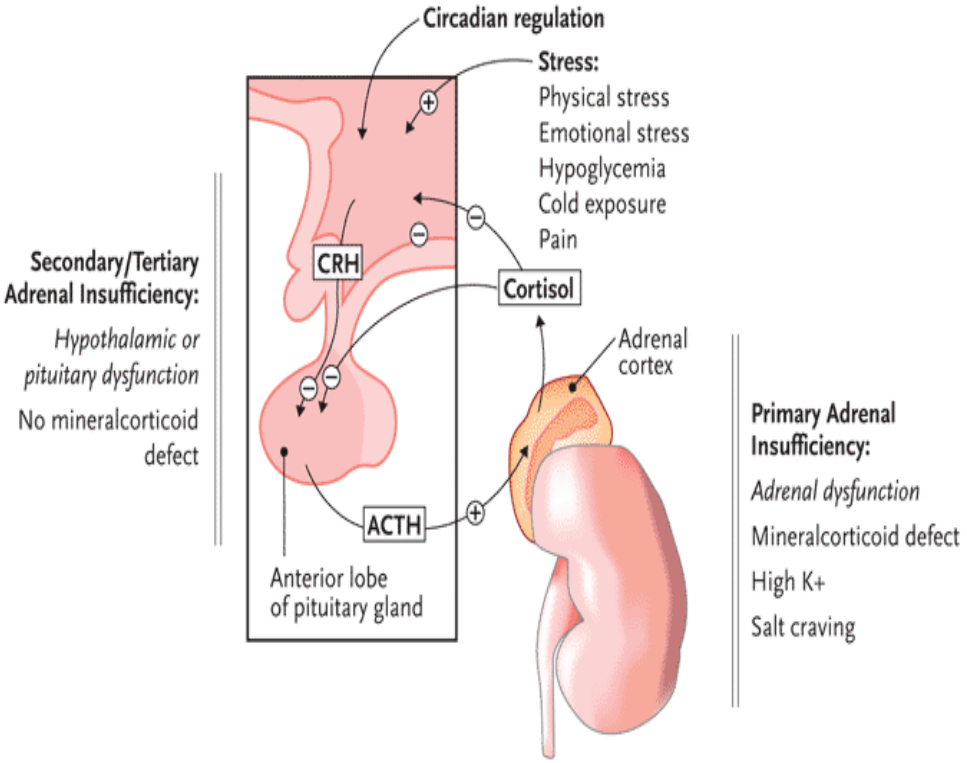
https://healedbybacon.files.wordpress.com/2015/11/addisons.png?w=607&h=661

Adrenal Insufficiency

Evaluation

Evaluating a patient with suspected AI is a three-step process:

- Establishing the diagnosis
- Differentiating between primary and secondary adrenal insufficiencies
- Looking for the cause of adrenal insufficiency.



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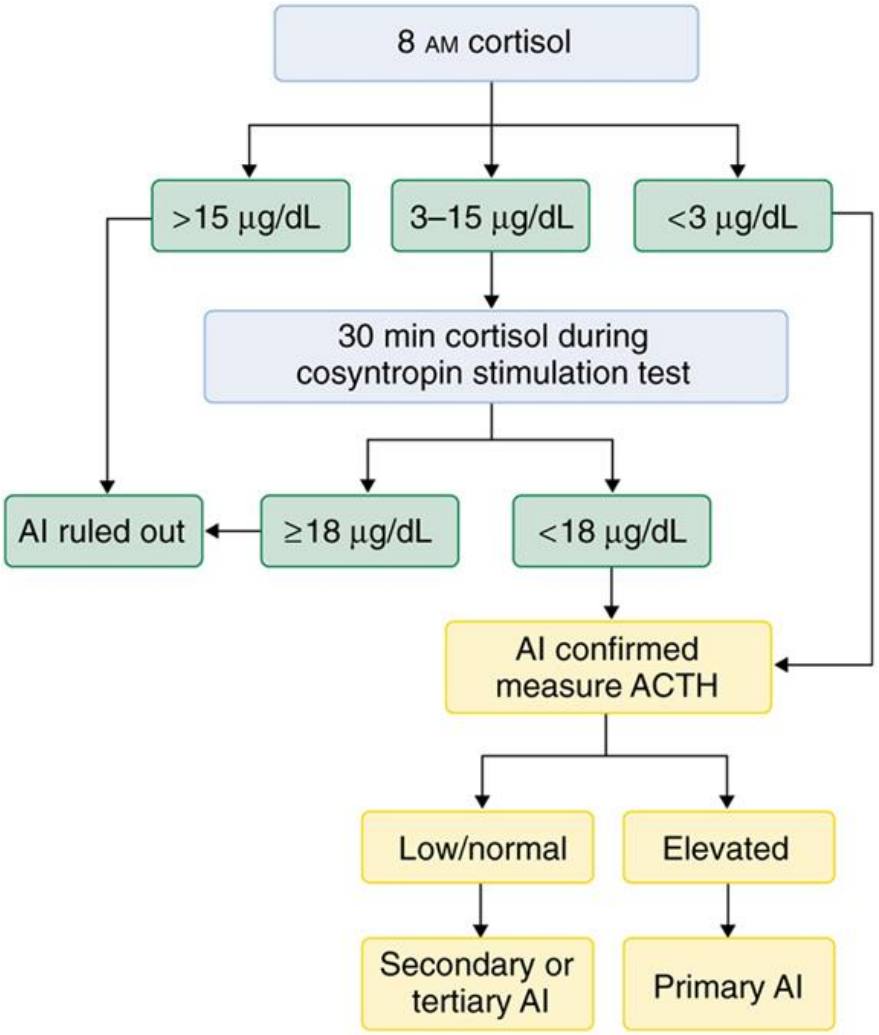
Adrenal Insufficiency

Diagnosis



- An early morning (8 am) plasma cortisol level lower than 3 µg/dL confirms AI, whereas a value higher than 15 µg/dL makes the diagnosis highly unlikely
- Cortisol levels in the range of 3 to 15 µg/dL may be seen in patients with primary, secondary, or tertiary adrenal insufficiency
- These patients should be evaluated by the cosyntropin (Cortrosyn) stimulation test (CST) at any time during the day.

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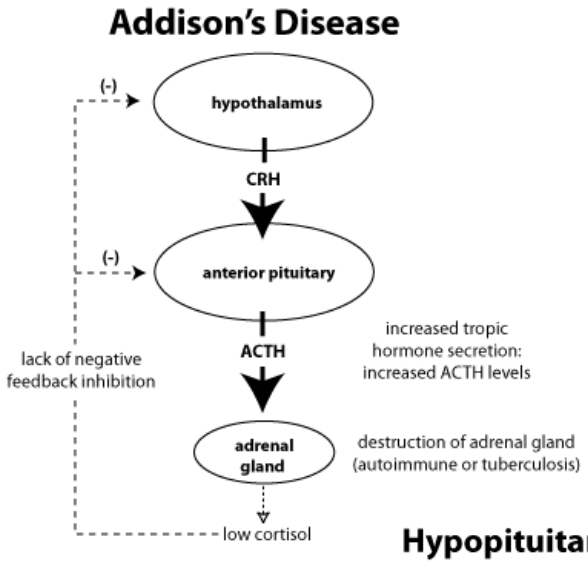
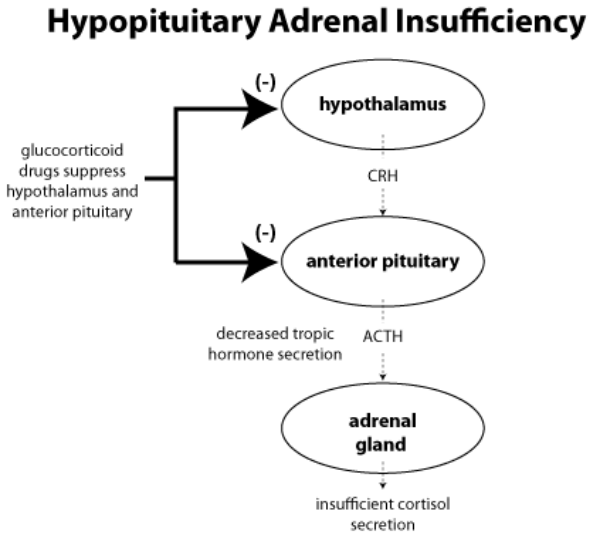
Adrenal Insufficiency

Differentiation Primary and Secondary Adrenal Insufficiencies

- Differentiation Between Primary and Secondary AI is done through the measurement of the basal plasma ACTH level
- An elevated ACTH level is consistent with primary AI
- A low or normal-range ACTH level, with a low cortisol level, confirms the diagnosis of secondary or tertiary AI.





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Adrenal Insufficiency

Determining the Cause of Adrenal Insufficiency

- When the biochemical workup is consistent with primary AI, computed tomography (CT) scanning of the adrenal glands may help with the differential diagnosis
- Enlarged adrenal glands or calcifications suggest an infectious, hemorrhagic, or metastatic cause
- In rare circumstances, CT-guided percutaneous fine-needle aspiration of enlarged adrenal glands may help establish the diagnosis
- Patients with tuberculous AI usually have evidence of active systemic disease
- Magnetic resonance imaging (MRI) of the pituitary gland is indicated if glucocorticoid therapy as the cause of the secondary AI has been ruled out.

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Adrenal Insufficiency

Treatment

- Patients with Addison's disease require lifelong replacement with glucocorticoids and mineralocorticoids; the dose is adjusted based on clinical status, including the presence or absence of orthostatic hypotension, hypertension, and electrolyte imbalance
- Patients with secondary or tertiary adrenal insufficiency do not need mineralocorticoid replacement
- Most patients can be educated to self administer hydrocortisone, and reduce the risk of an emergency room visit
- All patients should wear some form of identification indicating their adrenal insufficiency status.

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Adrenal Insufficiency

Alert Medical ID

For patients with AI, medical identification (ID) necklaces or bracelets are absolutely essential with information of their diagnosis and treatment regimen.

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Adrenal Insufficiency

Adrenal Crisis

- Adrenal crisis (acute AI) is a life-threatening emergency, which usually manifests with nausea, vomiting, abdominal pain, abdominal tenderness, fever, acute abdomen and shock
- Patients may be previously undiagnosed or have chronic primary AI, with no or inadequate glucocorticoid replacement
- Treatment of adrenal crisis should not be delayed
- Diagnostic workup in a patient with no history of AI should include a plasma sample for cortisol and ACTH level determination, immediately followed by an intravenous (IV) bolus of hydrocortisone, 100 mg, and adequate fluid replacement (normal saline)
- Hydrocortisone should be continued, 50 mg every 8 hours, while awaiting laboratory results.

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Adrenal Insufficiency

Adrenal Insufficiency in the Critically Ill Patient

- The overall incidence of AI in critically ill patients is less than 10%, but an incidence as high as 50% in a patient with septic shock has been reported
- Intensive care unit (ICU) patients with hemodynamic instability, despite fluid resuscitation (especially in the presence of shock), should be tested for AI
- Hydrocortisone, 50 mg IV every 6 to 8 hours is an adequate replacement dose for critically ill patients with suspected AI
- Treatment with this dose should be continued for 2 or 3 days
- After hemodynamic improvement, a gradual taper of hydrocortisone, depending on the patient's condition, should be instituted.

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Adrenal Hyperfunction

Selected List of Related Disorders

- Disorders related to adrenal hyperfunction (AH) are relatively rare, but they have significant mortality and morbidity if untreated
- When the adrenal glands produce too many hormones, the symptoms vary depending on the disorder
- Disorders related to AH include:
  - Cushing's syndrome
  - Primary hyperaldosteronism
  - Pheochromocytoma/Paraganglioma
  - Hormonally Active Tumors.

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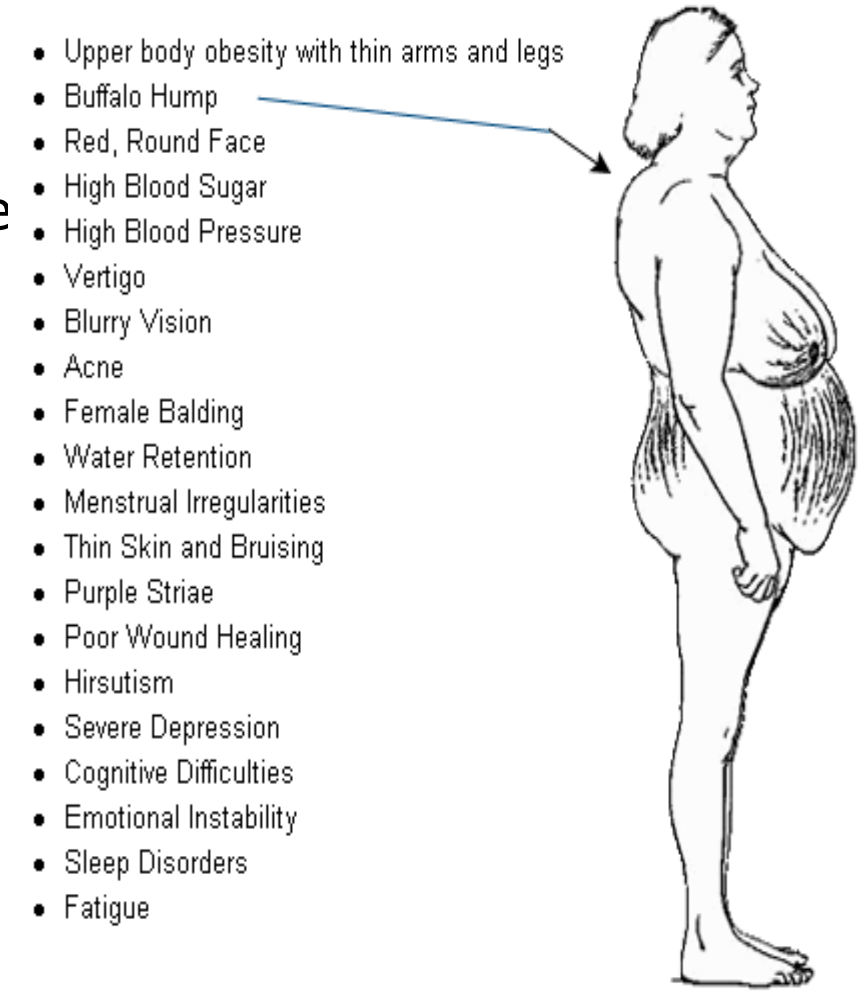
Adrenal Hyperfunction

Cushing's Syndrome: Definition and Classification

- Cushing's syndrome (CS) is composed of symptoms and signs associated with prolonge exposure to inappropriately high levels of plasma glucocorticoids
- Exogenous glucocorticoid intake is the most common cause of CS
- The endogenous causes are divided into ACTH-dependent and ACTH-independent CS.



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Adrenal Hyperfunction

Cushing's Syndrome: Etiology of Endogenous Form

ACTH-Dependent
Cushing's syndrome (67%)
Ectopic ACTH secretion (12%)
Ectopic CRH secretion (<1%)
ACTH-Independent
Adrenal adenoma (10%)
Adrenal carcinoma (8%)
Micro-and macronodular adrenal hyperplasias (1%)

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Adrenal Hyperfunction

Cushing's Syndrome: Clinical Features

Most Specific Signs & Symptoms	Less Specific Signs & Symptoms
plethora	papular acne
supraclavicular & dorsal fat pads	vellus hypertrichosis of face
central obesity	decreased libido/impotence
proximal muscle weakness	oligomenorrhea/amenorrhea
cutaneous wasting	infertility
purple striae	cutaneous & systemic fungal infections
spontaneous ecchymosis	poor wound healing
osteopenia	nephrolithiasis/polyuria
hypertension	headaches
early or delayed puberty (in children)	neuropsychiatric disorders
growth retardation (in children)	spinal epidural lipomatosis

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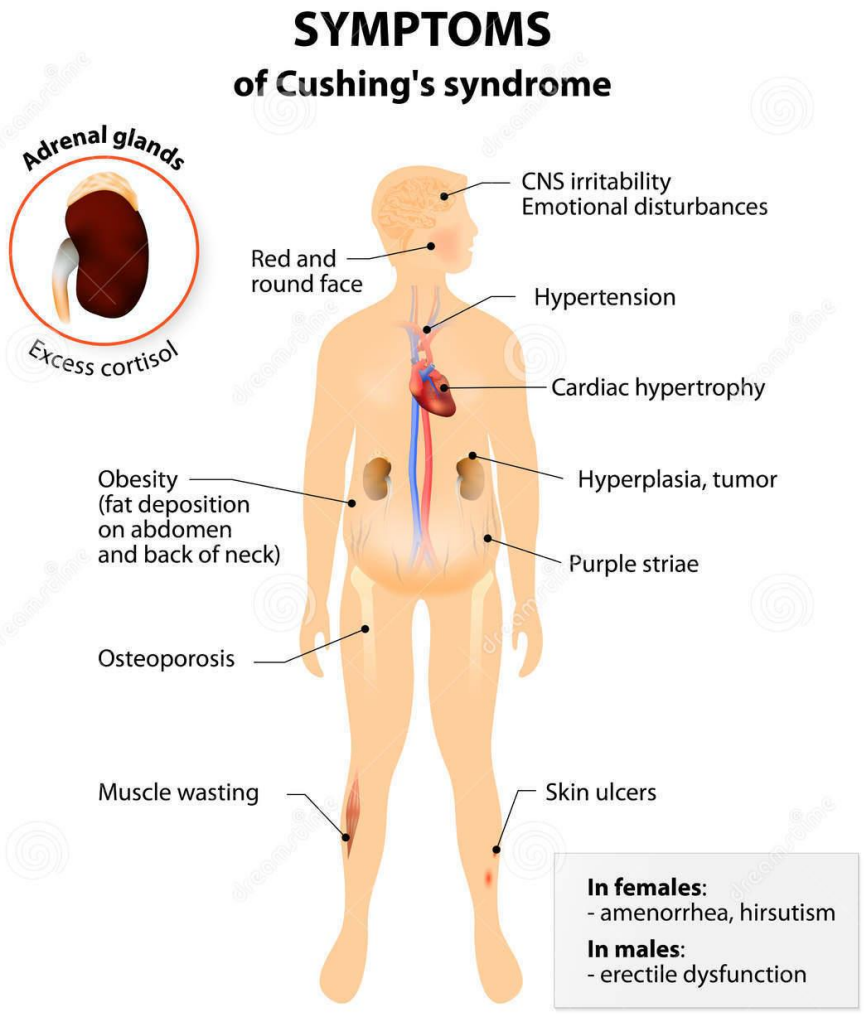
Adrenal Hyperfunction

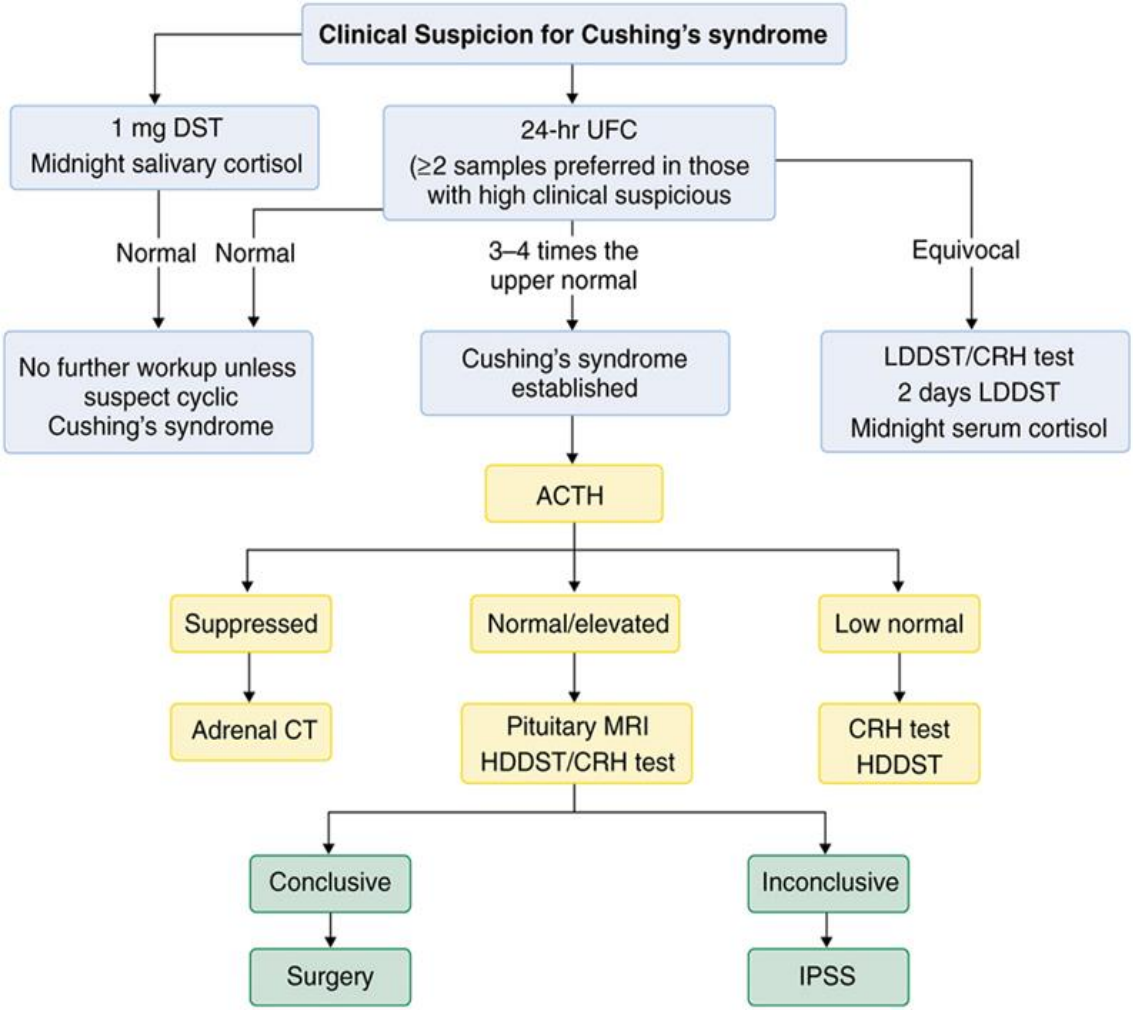
Symptoms, Signs and Laboratory Abnormalities



https://thumbs.dreamstime.com/z/cushings-disease-syndrome-signs-symptoms-cushing-s-labeled-human-silhouette-internal-organs-vector-illustration-55259613.jpg

Adrenal Hyperfunction

Cushing's Syndrome: Establishing the Diagnosis



- UFC - 24-hour urinary free cortisol determination
- DST - 1-mg dexamethasone suppression test
- Midnight salivary cortisol test
- LDDST - low dose dexamethasone suppression test
- IPSS - International Prognostic Scoring System

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Adrenal Hyperfunction

Cushing's Syndrome: Differential Diagnosis 1

- Once CS is biochemically confirmed, the plasma ACTH level should be measured, preferably in the morning
- A suppressed or low ACTH level (<10 pg/mL) is consistent with ACTH-independent CS and should be followed by adrenal CT scanning
- ACTH values of 10 to 20 pg/mL may be seen in patients with both adrenal and pituitary causes for CS; these patients should undergo a CRH stimulation test
- A flat response of ACTH to CRH during the test suggests an adrenal cause, but a more than 50% increase in the ACTH level during the test is consistent with Cushing's disease
- ACTH levels higher than 20 pg/mL suggest ACTH-dependent CS.

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Adrenal Hyperfunction

Cushing's Syndrome: Differential Diagnosis 2

- About 90% of patients with ACTH-dependent CS have a pituitary cause and the rest are ectopic in origin
- ACTH levels tend to be higher in ectopic CS compared with Cushing's disease, but there is significant overlap
- A more than 50% increase in the ACTH level after the CRH test and more than an 80% reduction in the morning cortisol level (8-9 am) after taking 8 mg dexamethasone at 11 pm during a high-dose DST is consistent with a pituitary source, and in the presence of a pituitary adenoma, almost establishes the definitive diagnosis of CS.

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Adrenal Hyperfunction

Cushing's Syndrome: Differential Diagnosis 3

- . If the CRH stimulation test and DST results are not concordant and MRI does not show a pituitary adenoma, then inferior petrosal sinus sampling to distinguish ectopic from Cushing's disease is indicated
- Localizing tumors that produce ectopic ACTH is accomplished by chest and abdominal CT studies, followed by neck CT if no source is found
- An octreotide scan may be of some value in patients with ectopic CS and negative imaging studies.

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Adrenal Hyperfunction

Cushing's Syndrome: Treatment

- Surgical (trans-sphenoidal) removal of the ACTH-secreting pituitary tumor is the treatment of choice
- CS caused by an adrenal adenoma is usually cured by laparoscopic unilateral adrenalectomy
- Adrenal carcinoma is an aggressive tumor with a poor prognosis; surgical resection at an early stage, along with lifelong mitotane therapy soon after surgery, offers the only chance for cure or long-term remission
- Surgical removal of an ectopic ACTH-producing tumor results in cure
- Medical therapy with ketoconazole, metyrapone, aminoglutethimide, or mitotane may be considered for patients with a limited life expectancy or for alleviation of hypercortisolemic symptoms before surgery.

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Primary Hyperaldosteronism

Prevalence

- Conn first described primary hyperaldosteronism (PH) in 1955 in a patient with an adrenal adenoma
- A prevalence as high as 10% in hypertensive patients, and women in their fourth to sixth decade of life are affected more often than men
- A solitary aldosterone-producing adenoma (65%) and bilateral idiopathic hyperplasia (30%) are the most common subtypes of PH
- The adenomas are usually benign and smaller than 2 cm in diameter
- Idiopathic adrenal hyperplasia may be accompanied by adrenocortical nodules and is associated with lower aldosterone levels and less severe hypertension, compared with adenomas.

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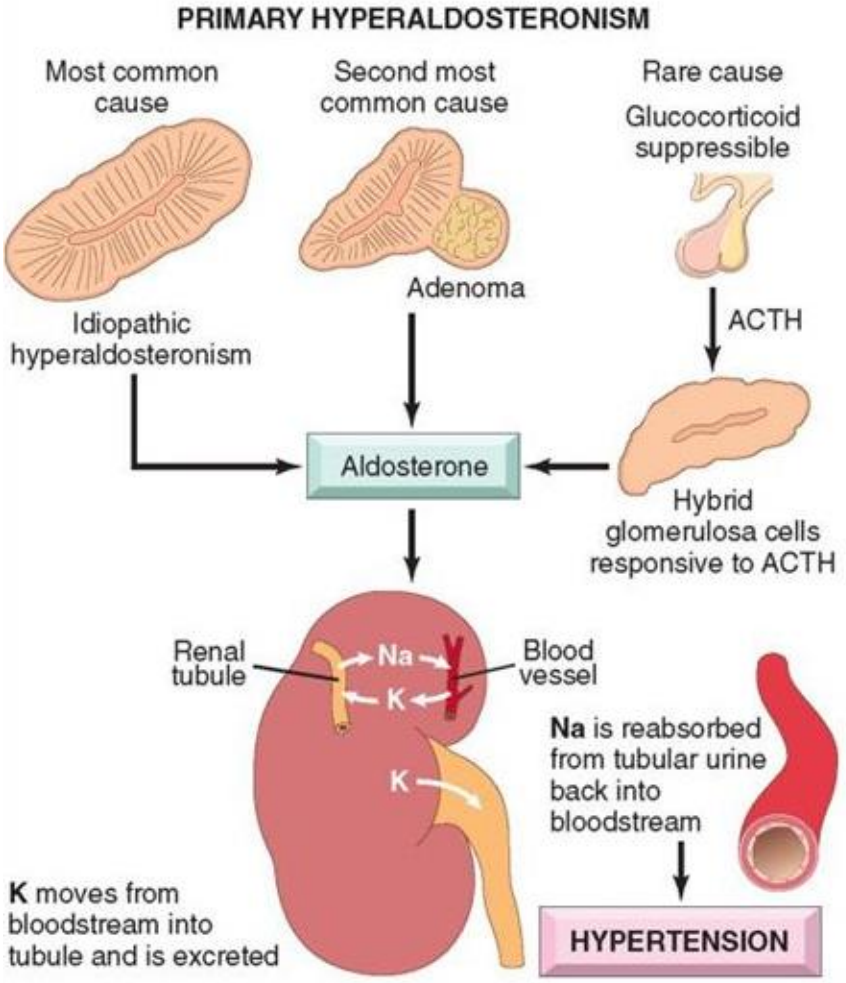
Primary Hyperaldosteronism

Causes



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Primary Hyperaldosteronism

Forms of Familial Hyperaldosteronism

Two forms of familial primary hyperaldosteronism (FH) have been described:

- FH type I, or glucocorticoid-remediable hyperaldosteronism (GRH), is an autosomal dominant disease characterized by a chimeric gene between the 11β-hydroxylase and aldosterone synthase, with varying degrees of hyperaldosteronism, which responds to exogenous glucocorticoids
- FH type II is an autosomal dominant disorder of both the aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism (IHA).

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Primary Hyperaldosteronism

Clinical Presentation

- The clinical picture varies from asymptomatic to symptoms related to hypertension, hypokalemia, or both
- Patients may have headaches, polyuria, nocturia, polydipsia, parasthesias, weakness, and muscle cramps
- There are no specific physical findings
- The degree of hypertension is usually moderate to severe, and may be refractory to conventional antihypertensive agents
- Malignant hypertension and leg edema are rare
- The left ventricular hypertrophy is disproportionate to the level of blood pressure and improves after treatment of PH, even if hypertension persists.

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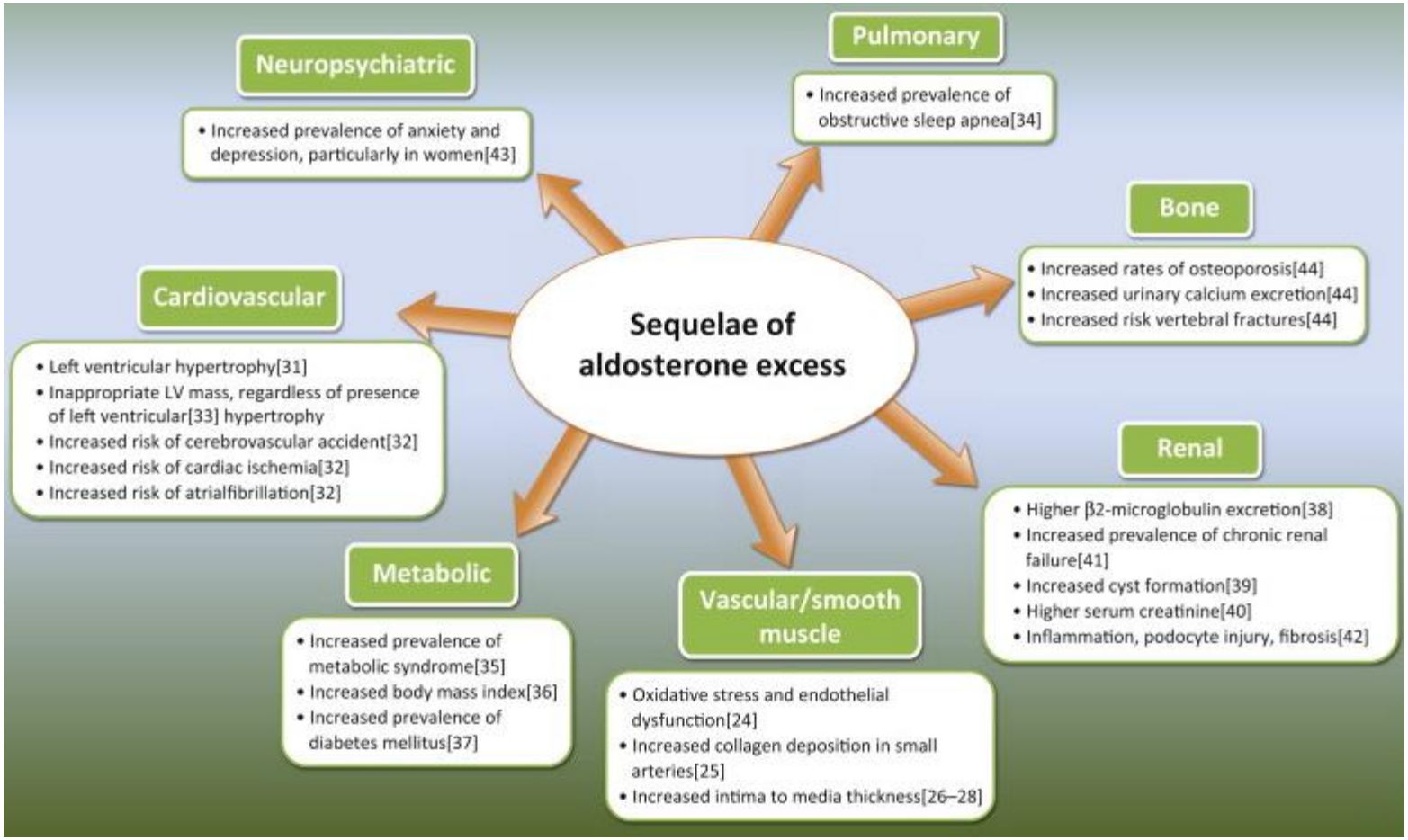
Primary Hyperaldosteronism

Signs and Symptoms



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Primary Hyperaldosteronism

laboratory Tests

- Routine laboratory tests may show slightly high serum sodium levels (143-147 mEq/L), hyperglycemia, hypokalemia, metabolic alkalosis, and hypomagnesemia
- Although most patients with hyperaldosteronism are not hypokalemic, a low serum potassium level may be noted, either spontaneously or after thiazide or loop diuretic use
- Hypokalemia may be severe and difficult to correct
- Hypokalemia presence reduces the secretion of aldosterone and thus should be corrected before the laboratory evaluation of hyperaldosteronism.

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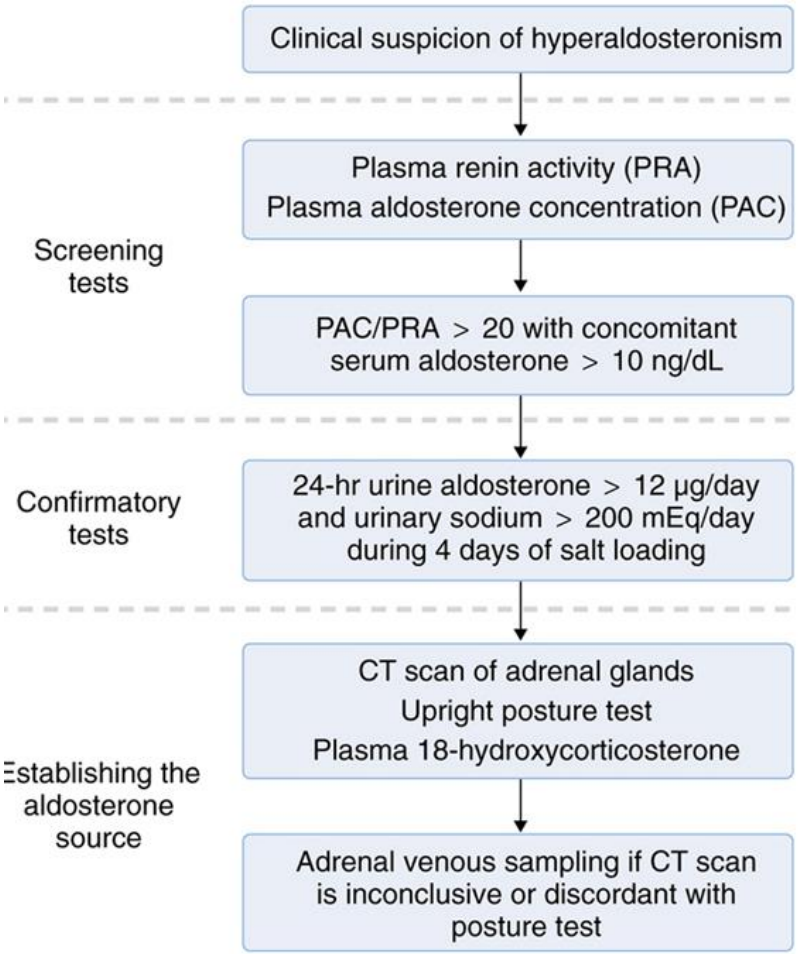
Primary Hyperaldosteronism

Diagnosis



- The workup of a patient for PH involves the following steps: screening tests for PH, establishing the autonomy of aldosterone secretion, and determination of the source of hyperaldosteronism
- The categories of patients:
  - hypertensive with spontaneous or thiazide-induced hypokalemia
  - hypertensive resistant to therapy
  - hypertensive with adrenal incidentalomas.

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Primary Hyperaldosteronism

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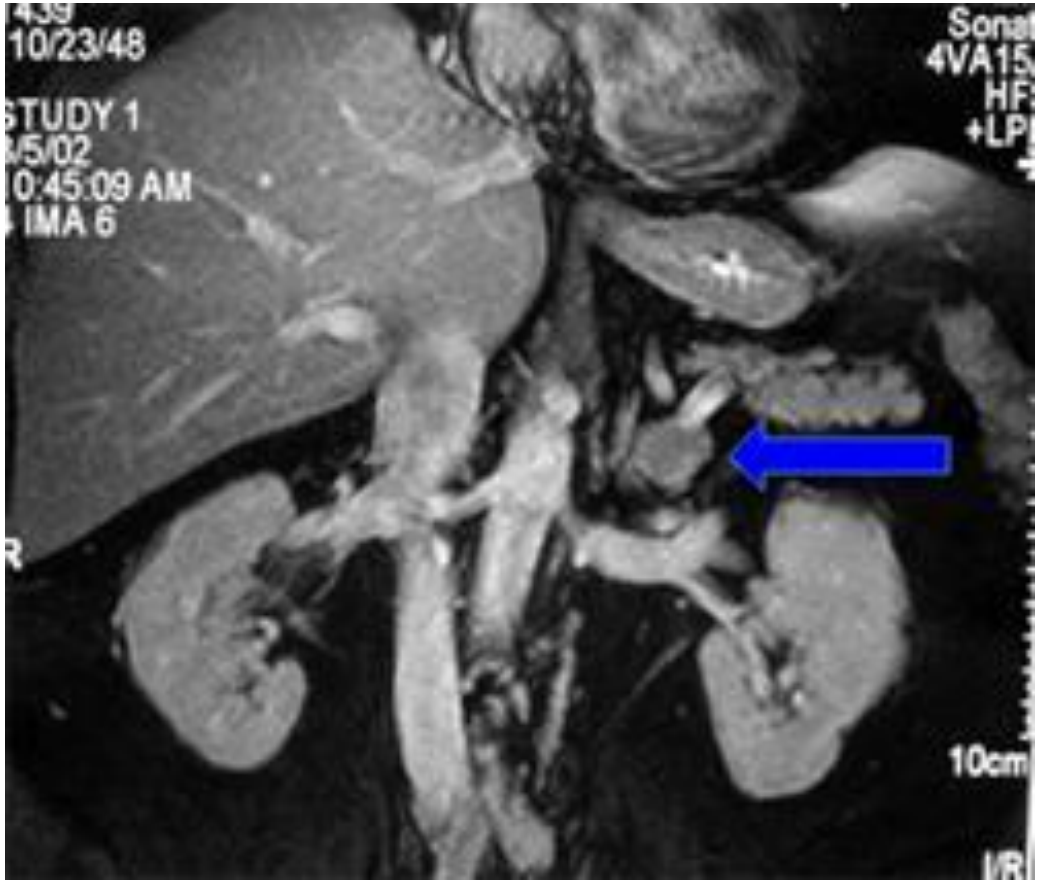

Adrenal adenoma on Computer Tomography

http://columbiasurgery.org/conditions-and-treatments/primary-hyperaldosteronism-conns-syndrome

Primary Hyperaldosteronism

Screening Tests

- Although hypokalemia in a hypertensive patient is suggestive of hyperaldosteronism, normokalemia does not exclude the diagnosis
- Measurement of the 24-hour urinary potassium level can be useful in assessing the cause of a low potassium level
- Urinary potassium excretion >30 mEq/24 hours in a patient with hypokalemia suggests PH, if plasma renin activity (PRA) is low
- The ratio of the plasma aldosterone concentration (PAC) to PRA (PAC/PRA) is the best screening test for PH
- Spironolactone and eplerenone should be discontinued for 6 weeks before testing
- Low or suppressed PRA during therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) suggests hyperaldosteronism.

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Primary Hyperaldosteronism

Differentiating Aldosterone-Producing Adenoma From Idiopathic Hyperaldosteronism

Parameter	APA	IHA
HTN, potassium concentration [K^+]	HTN more severe, higher likelihood of hypokalemia	HTN less severe, less likelihood of hypokalemia
Upright posture test	Decrease or <30% increase of serum aldosterone level	Increase by >30% of serum aldosterone level
18-Hydroxycorticosterone	>100 ng/mL	<100 ng/mL
Computed tomography scan	>1-cm adrenal tumor, with normal contralateral adrenal	No adrenal tumor, bilateral thickening of adrenals
Bilateral adrenal venous sampling	Lateralization	No lateralization

APA, aldosterone-producing adenoma; HTN, hypertension; IHA, idiopathic hyperaldosteronism

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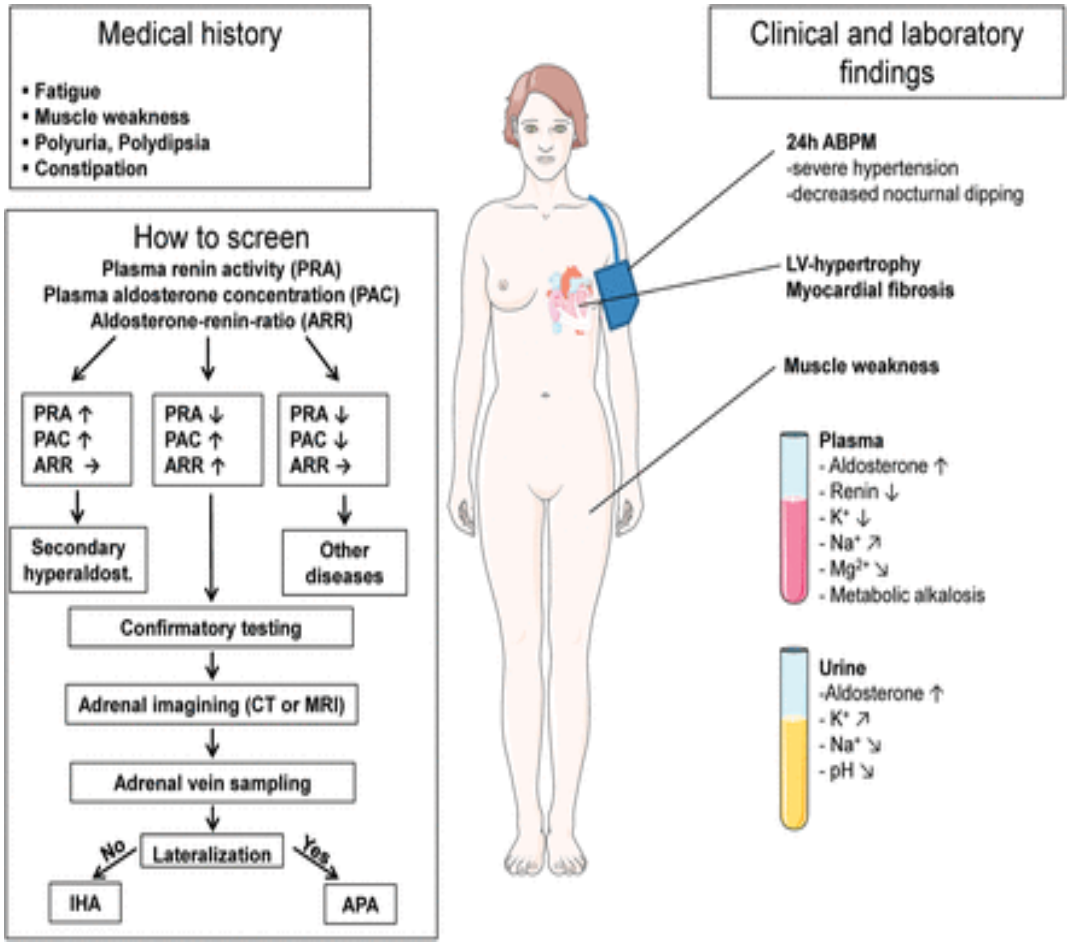
Primary Hyperaldosteronism

Medical History, Clinical Findings, and Screening Work-Up



Patient with suspected primary aldosteronism. PRA, plasma renin activity; PAC, plasma aldosterone concentration; ARR, aldosterone–renin ratio; 24 h-ABPM, 24 h ambulatory blood-pressure monitoring; LV, left ventricular; K^+, potassium; Na^+, sodium; Mg^{2+}, magnesium; APA, aldosterone-producing adenoma; IHA, idiopathic hyperaldosteronism.

http://eurheartj.oxfordjournals.org/content/35/19/1245

Primary Hyperaldosteronism

Treatment

- The treatment goals are to reduce the morbidity and mortality
- Unilateral adrenalectomy results in normalization of hypokalemia and improvement in hypertension in all patients
- Medical treatment is reserved for patients with IHA or those with APAs who are poor surgical candidates
- Spironolactone or Eplerenone is the treatment of choice
- Side effects include painful gynecomastia, nausea, headaches, impotence, and irregular menstruation; Eplerenone that blocks the aldosterone receptor selectively has a better side effect profile
- The use of a mineralocorticoid is usually not necessary.

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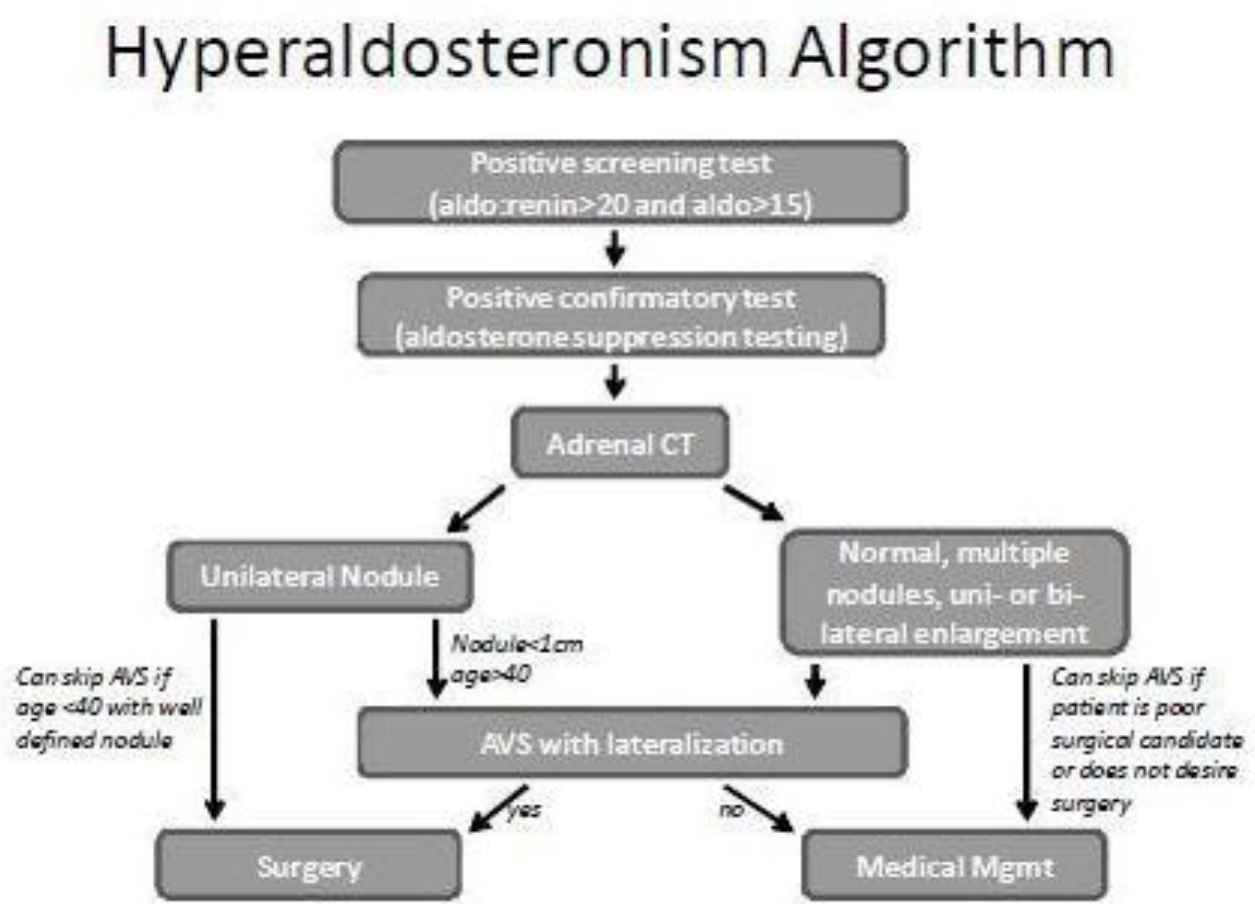
Primary Hyperaldosteronism

Diagnosis and Treatment Algorythm



https://s3.amazonaws.com/classconnection/949/flashcards/3738949/jpg/hy-14926404BA85D6DBA4F.jpg

Primary Hyperaldosteronism

Glucocorticoid-Remediable Hyperaldosteronism

- Familial hyperaldosteronism type I, or glucocorticoid-remediable hyperaldosteronism (GRH) individuals are younger 40 years, exhibit hypertension resistant to standard therapy, and have a family history of primary hyperaldosteronism or a cerebrovascular accident at a young age
- Most have a normal serum potassium level
- A very high urinary 18-hydroxycortisol level (>3000 nmol/24 hr) or genetic testing to detect a chimeric gene establishes the diagnosis
- Affected individuals should have neurovascular screening for cerebral aneurysms
- Treatment with glucocorticoids, eplerenone, spironolactone, amiloride, and triamterene is effective.

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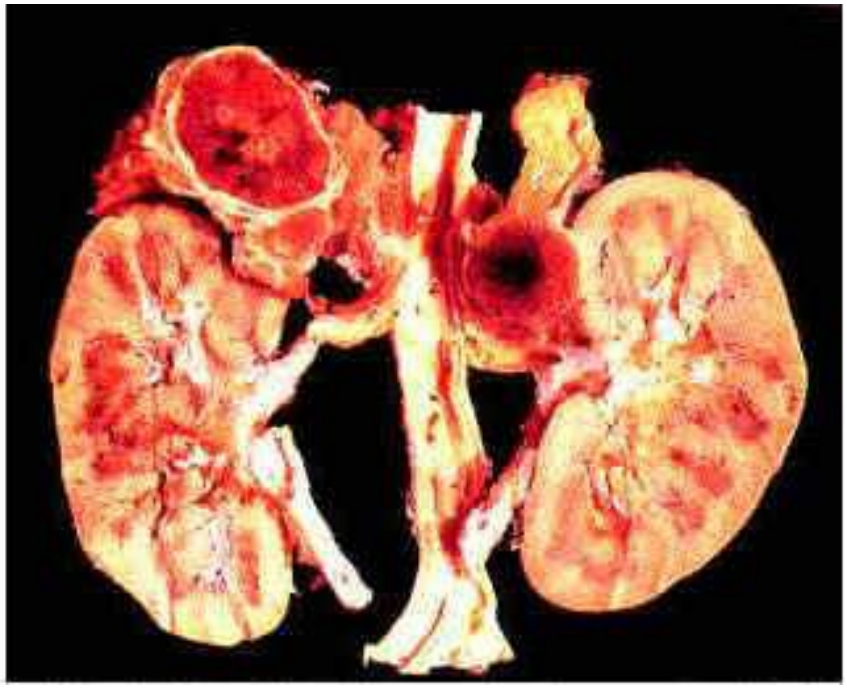
Pheochromocytoma

Definition

- Pheochromocytomas (PHEOs) are rare chromaffin cell tumors that may occur at any age
- Although their true prevalence is unknown, they occur in about 0.3% of hypertensive patients
- If untreated, PHEOs can have severe consequences, such as myocardial infarction, heart failure, cerebrovascular accident, and death.



http://health-pictures.com/images/Pheochromocytoma.jpg clevelandclinicmeded.com/medicalpubs/diseasemanagement/endocrinology/diseases-of-the-adrenal-gland/

Pheochromocytoma

Anatomic Considerations and Etiology

- Most PHEOs are benign, sporadic, unilateral, and located within the adrenal gland
- Extra-adrenal PHEOs (paragangliomas) occur in about 15% of cases in the superior and inferior para-aortic areas, including the Zuckerkandl organ, bladder, thorax, and head, neck, and pelvis
- Paragangliomas tend to occur in younger patients <20 years); they are multifocal in about 15% to 30% of cases
- Bilateral PHEOs are usually seen as part of familial syndromes
- Malignant PHEOs have a higher prevalence in ectopic PHEOs and lower prevalence in familial PHEOs
- About 10% to 15% of PHEOs are hereditary in nature.

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Pheochromocytoma

Clinical Manifestations

- Patients with PHEO may have paroxysmal hypertension (48%) or persistent hypertension (29%), or be normotensive (13%).
- Wide fluctuations in blood pressure and resistance to antihypertensive medications are typical of those with PHEO
- The triad of headaches, palpitations, and diaphoresis suggests the diagnosis of PHEO, but absence of these symptoms does not exclude the disease
- Attacks are usually precipitated by emotional stress, exercise, anesthesia, abdominal pressure, or ingestion of tyramine-containing foods
- Symptoms include pallor, flushing, orthostatic hypotension, weight loss, dyspnea, polyuria, polydipsia, visual blurring, focal neurologic symptoms, and change in mental status.

http://health-pictures.com/images/Pheochromocytoma.jpg clevelandclinicmeded.com/medicalpubs/diseasemanagement/endocrinology/diseases-of-the-adrenal-gland/

Pheochromocytoma

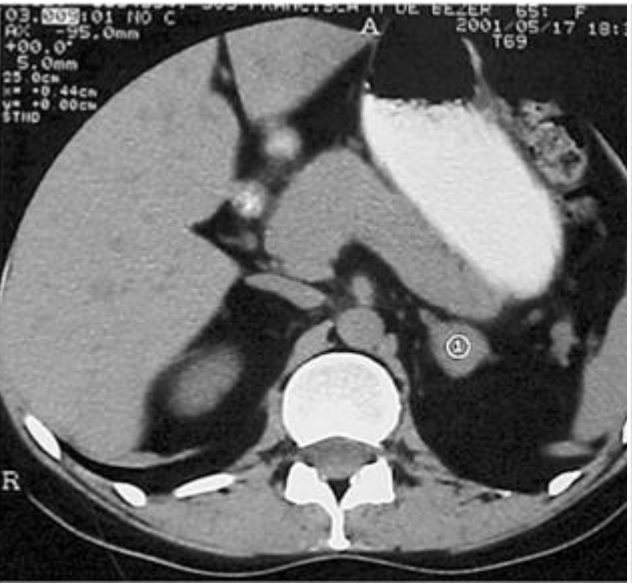
Diagnosis

- The diagnosis can be established by measuring catecholamines and metanephrines in plasma (blood) or through a 24-hour urine collection
- Care should be taken to rule out other causes of adrenergic (adrenalin-like) excess like hypoglycemia, stress, exercise, and drugs affecting the catecholamines like stimulants, methyldopa, dopamine agonists, or ganglion blocking antihypertensives
- Various foodstuffs (e.g. coffee, tea, bananas, chocolate, cocoa, citrus fruits, and vanilla) can also affect the levels of urinary metanephrine and VMA (vanillylmandelic acid)
- Imaging studies of the head, neck, and chest, and abdomen can help localize the tumor.

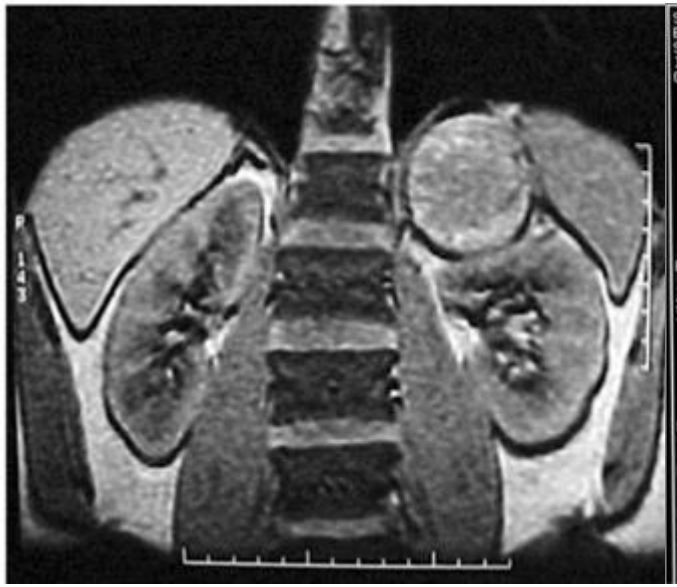
https://en.wikipedia.org/wiki/Pheochromocytoma#Diagnosis

Pheochromocytoma

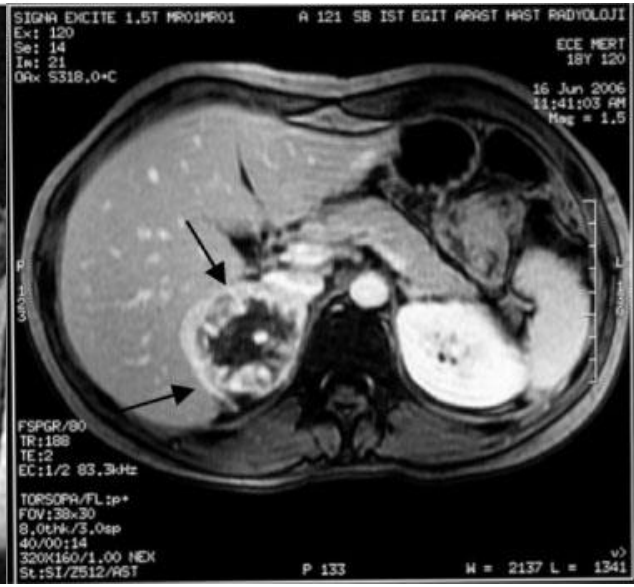
Imaging Studies



Computer tomography showing a 2 cm left adrenal mass



Magnetic resonance imaging showing large adrenal mass



Magnetic resonance imaging showing large right adrenal mass (arrows)

http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1677-55382009000100005

Pheochromocytoma

Treatment

- Surgical resection of the tumor is the treatment of first choice
- Either surgical option requires prior treatment with the non-specific and irreversible alpha adrenoceptor blocker phenoxybenzamine or a short acting alpha antagonist (e.g. prazosin, terazosin, or doxazosin)
- Once the pheochromocytoma has been resected, thereby removing the major source of circulating catecholamines, a situation arises where there is both very low sympathetic activity and volume depletion; this can result in profound hypotension
- Therefore, it is usually advised to "salt load" pheochromocytoma patients before their surgery.

https://en.wikipedia.org/wiki/Pheochromocytoma#Diagnosis

Adrenal Hyperandrogenism

The Adrenal Glands as the Source of Androgens

- The adrenal glands are an important source of androgens, especially in children and women
- The primary adrenal androgens, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS sulfate), are under ACTH control and have little intrinsic androgenic activity
- However, they are converted to androstenedione and then to testosterone (and estrogen) in both the adrenal gland and peripheral tissues
- DHEA and DHEA sulfate are responsible for adrenarche (pubic hair development)
- Peak levels occur in the third decade of life and decline progressively to 25% of peak levels around the age of 80 years.

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Adrenal Hyperandrogenism

Clinical Manifestations in Childhood

- In female neonates, androgen excess causes female pseudohermaphroditism (ambiguous genitalia)
- Male infants exhibit penile enlargement
- At prepuberty androgen excess manifests as increased rate of growth in height and skeletal maturation with premature epiphyseal fusion and short adult height; boys exhibit penile enlargement, hair growth in androgen-dependent areas, deepening of the voice, and other secondary sexual characteristics; girls have hirsutism, acne, and clitoromegaly
- At puberty androgen excess causes premature skeletal maturation and short adult height in boys, and amenorrhea, different degree of virilization, and increased skeletal maturation, resulting in short adult height In girls.

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Adrenal Hyperandrogenism

Clinical Manifestations in Adults

- In men, a decrease in size of the testicles, testosterone secretion, and spermatogenesis caused by inhibition of gonadotropin secretion may occur
- In women, hirsutism, acne, menstrual irregularities, male pattern baldness, infertility, decreased breast tissue, increased muscle mass, android body habitus, and clitoromegaly may occur.

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Adrenal Hyperandrogenism

Management

- Management of hyperandrogenism symptoms
- The use of antiandrogens such as cyproterone acetate, spironolactone, and flutamide
- Cyproterone acetate is a synthetic steroidal antiandrogen, progestin, and antigonadotropin
- Spironolactone is aldosterone antagonists
- Flutamide is a synthetic, non-steroidal antiandrogen

en.wikipedia.org/wiki/Hyperandrogenism clevelandclinicmeded.com/medicalpubs/diseasemanagement/endocrinology/diseases-of-the-adrenal-gland

Nonclassic Congenital Adrenal Hyperplasia

- Nonclassic congenital adrenal hyperplasia is characterized by milder enzyme dysfunction and manifests commonly in adolescence or adulthood
- Although some patients with NCAH may be asymptomatic, hirsutism is the most common symptom
- The ACTH stimulation test is the best screening test for evaluating adrenal gland functions
- Asymptomatic patients with NCAH do not need glucocorticoid treatment
- If the main concern of the patient is infertility, ovulation induction is the treatment of choice
- If the patient seeks medical advice because of hirsutism, anti-androgens may be used.

http://www.ncbi.nlm.nih.gov/pubmed/17551465

Androgen-Secreting Adrenal Tumors

- Primary adrenocortical carcinoma may be associated with excess androgen secretion, and sometimes cortisol may also occur
- Primary adrenocortical carcinoma is a rare disease, with an incidence of 1 per 600,000 to 1,600,000 and a prevalence of 4 to 12 per 1,000,000
- Female patients may exhibit virilization with very high levels of DHEA sulfate (500 µg/dL or higher), testosterone, and urinary 17-ketosteroids
- Primary adrenocortical carcinomas are highly malignant, with a poor prognosis
- Tumors are usually larger than 6 cm, invade the capsule, metastasize early, and typically recur after surgery.

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Adrenal Incidentaloma

- Adrenal masses are often discovered incidentally and are then termed adrenal incidentalomas
- The differential diagnosis of adrenal incidentaloma includes many primary, metastatic, benign, and malignant entities
- The treatment for a hormonally active (functional) adrenal incidentaloma is surgery
- The treatment for a malignancy depends on the cell type, spread, and location of the primary tumor
- Nonfunctional adrenal incidentaloma is not premalignant, and surgical excision is not indicated.

http://emedicine.medscape.com/article/116587-overview

Considerations of the Pharmacologic use of Glucocorticoids

- Pharmacologic doses of synthetic glucocorticoids are used in a wide variety of diseases for their anti-inflammatory and immunosuppressive effects
- Two main clinical problems arise with the chronic use of pharmacologic doses of glucocorticoids, iatrogenically induced Cushing's syndrome and adrenal insufficiency on abrupt cessation of therapy
- Alternate-day therapy and avoidance of nighttime doses are associated with less suppression of the hypothalamic–pituitary–adrenal axis after discontinuation of glucocorticoid therapy.

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Prognosis and Prophylaxis

- Prognosis depends strictly from the diseases nature, their clinical manifestations, quality of treatment and compliance of all its prescriptions
- There are no known lifestyle changes to lower the risk of developing essential adrenal gland disorders
- The following dietary and lifestyle considerations may support healthy adrenal function: avoiding simple carbohydrates, calorie restriction, limiting stimulants, exercising, maintaining a positive outlook and good self esteem, adequate sleep at regular intervals, etc.

http://www.lifeextension.com/Protocols/Metabolic-Health/Adrenal-Disorders/Page-07

Abbreviations

ACTH – adrenocorticotropic hormone

AI - adrenal insufficiency

AIDS - acquired immune deficiency syndrome

AH - adrenal hyperfunction

APA - aldosterone-producing adenoma

DST - 1-mg dexamethasone suppression test

CRH - corticotropin-releasing hormone

CS - Cushing's syndrome

CST - cosyntropin (Cortrosyn) stimulation test

CT - computed tomography

DHEA - dehydroepiandrosterone

DHEAS - dehydroepiandrosterone sulfate

ICU -intensive care unit

ID – identification

IHA - idiopathic hyperaldosteronism

IV – intravenous

IPSS - International Prognostic Scoring System

FH - familial hyperaldosteronism

GRH - glucocorticoid-remediable hyperaldosteronism

LDDST - low dose dexamethasone suppression test

MRI - magnetic resonance imaging

NCAH - nonclassic congenital adrenal hyperplasia

PH – primary hyperaldosteronism

UFC - 24-hour urinary free cortisol determination

Diagnostic and Treatment Guidelines

- Adrenal Insufficiency and Addison's Disease
- Clinical Guidelines for the Diagnosis and Treatment of Cushing's Disease in Korea
- Addison's Disease: New Guideline Details Diagnosis and Treatment
- Addison Disease: Early Detection and Treatment Principles
- Diseases of the Adrenal Gland