Adrenal Incidentaloma and Adrenal Hormonal Secretion

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Disclosure

Consultant: Corcept Therapeutics, Moderna, Novo Nordisk, Recordarti

Research Grant: Crinetics; Recordarti;

Speakers Bureau: Amhryt; Ascendis; Moderna; Recordarti

Other: CDC/CMSS Grant, Veteran's Administration Grant, Primary Hyperaldosteronism Guidelines Endocrine Society; TF Member; Chair; AACE Oversight Guidelines Committee and Board of Director; Chair, Special Interest Group, Pituitary and Adrenal, ACP Board of Regents; EFF Board of Director

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Adrenal Incidentaloma (AI)
Lesion > 1cm

Endocrine Diagnosis
5% in Adults

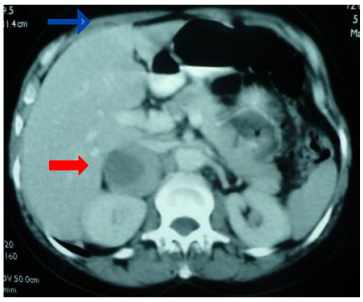
NON-SUSPECTED Lesion

Etiology

Benign or Malignant?
Functioning?

Not included:

- Oncology patients in the process of staging
- Patients with a genetic history of predisposing syndromes to adrenal tumors



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Clinical Relevance

- ➔ The **study of AI** is justified in order **to rule out** pheochromocytoma, adrenal carcinoma, excess cortisol and aldosterone (in arterial hypertension).
- ➔ Patients with **mild autonomous cortisol secretion (MACS)** have a **higher prevalence** of cardiovascular risk factors and metabolic bone disease.
- ➔ Small, non-functioning adrenal tumors with low CT attenuation **do not justify** intervention or long-term follow-up.
- ➔ **Most patients can be reassured and discharged** once malignancy and hormonal hypersecretion have been ruled out.

E. Kebebew. Adrenal Incidentaloma. NEJM 2021, 384; 1542
Sherlock et al. Adrenal Incidentaloma. Endocrine Reviews. 2020, 41(6):775–820

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Epidemiology and Prevalence

Prevalence 5%

< 1% under 30 yo
> 7% older than 70 yo

Varies according to data and patient selection

METASTASIS	PREVALENCE
Patients without an oncology history	5-7%
Patients with a cancer history (**lung, kidney, GI, breast, and melanoma**)	50-75%

ADENOMA ➔ NOT functioning (75%) ➔ **CORTISOL secretor (12%)** ➔ ALDOSTERONOMA secretor (2.5%)	**80%**
Pheochromocytoma	7-10%
Adrenocortical Carcinoma Metastasis Other injuries (myelolipomas, cysts, ganglioneuromas)	4-8% 5-7% 5-7%

Bilateral AI 10-15%

Terzolo et al. Eur J Endocrinol (2011): 164: 851-870
Mantero et al. A Survey in Adrenal Incidentaloma in Italy. JCEM. 2000
Sherlock et al. Adrenal Incidentaloma. Endocrine Reviews, 12, 2020, 41(6):775–820

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Extra-adrenal Injuries

- ❑ Ectopic Spleen
- ❑ Paraganglioma
- ❑ Renal, pancreatic, hepatic, stomach (GIST), colon injuries
- ❑ Vascular (aneurysms, other)

Otras Lesiones

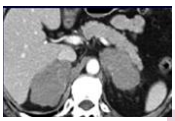
- ❑ Cysts
- ❑ Myelolipoma
- ❑ Ganglioneuroma
- ❑ Schwannomas

Spectrum of Different Pathologies that Share the Same Discovery Pathway

Adrenal or Extra-adrenal?

¿Benign or Malignant?
Cortex, Medulla, Extra-Adrenal

¿Hormonally Functioning?

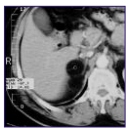


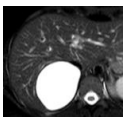
Bilateral Masses 10-15%

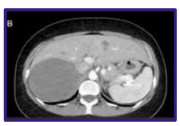
- Pheochromocytoma
- Cortical adenomas
- Macronodular hyperplasia
- Congenital adrenal hyperplasia
- Metastasis
- Lymphoma
- Infections
- Hemorrhage
- Amyloidosis

Images

Biochemistry







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Causes of Adrenal Lesions

	Non-functioning	Functioning
Benign	**Adenoma** Myelolipoma Ganglioneuroma Hemangioma/Hematoma Cysts Infections (TBC)	**Adenoma** Micro and macronodular disease Aldosteronism
Malignant	**Adrenal carcinoma** Lymphoma Sarcoma Neuroblastoma/ ganglioneuroblastoma Metastasis	**Adrenal carcinoma** Pheochromocytoma

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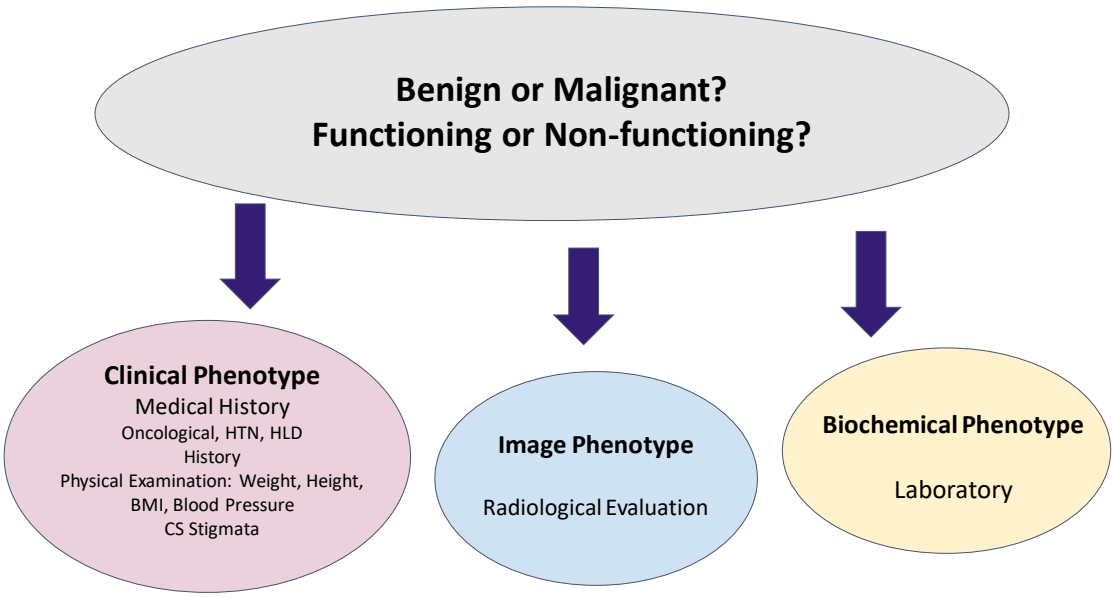

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Radiological Evaluation

Benign or Malignant?

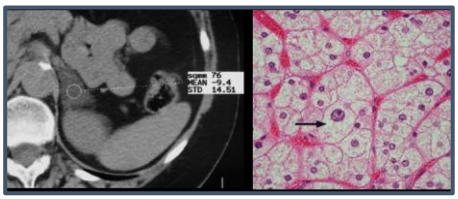
Intracellular fat:
- ➔ 90% of incidentalomas
- ➔ Well-circumscribed, round and homogeneous mass
- ➔ **Fat content:** 70% high (< 10 UH)
- ➔ 30 % low (10–40 UH)
- ➔ Late phase wash out > al 50 %

What do we assess?
Lipid content

How do we assess?
Non-contrast CT (first line)

Size vs density

What are we measuring?
Hounsfield UH units



Spontaneous density < 10 UH

E. Kebebew. Adrenal Incidentaloma. NEJM 2021, 384; 1542

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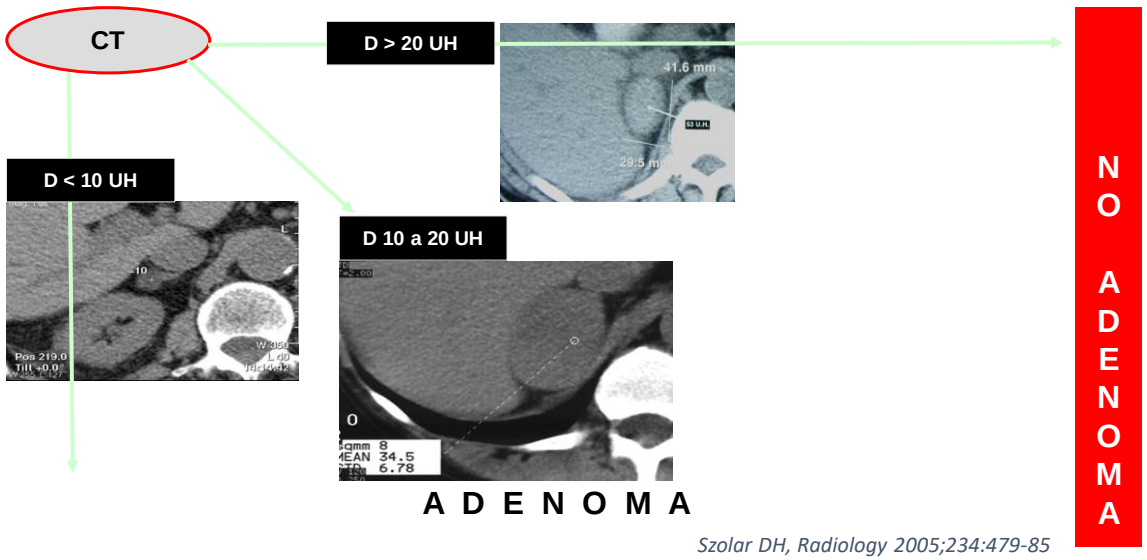
Computed Tomography: Density



Szolar DH, Radiology 2005;234:479-85

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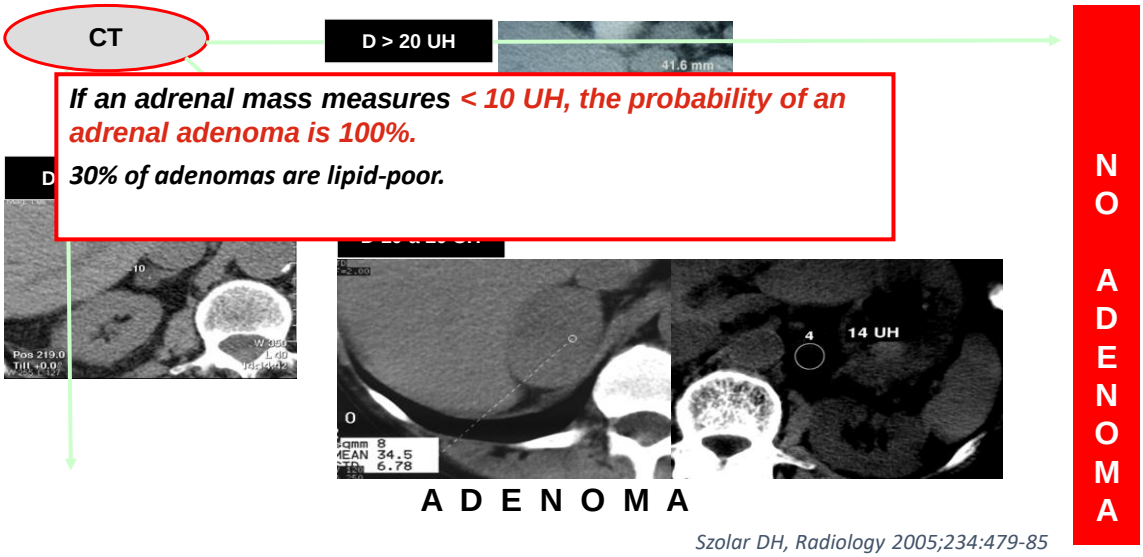

Szolar DH, Radiology 2005;234:479-85

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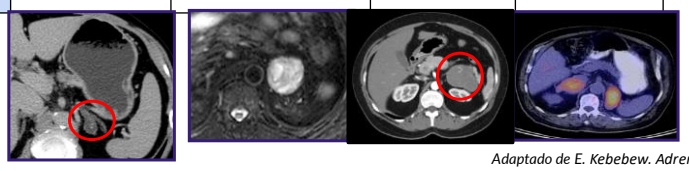
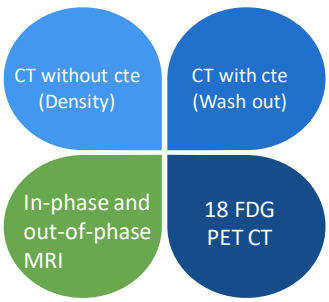
	Adenoma	Pheochromocytoma	ACC	Metastasis
Characteristics	Clear edges	Clear edges	Irregular	Irregular, uni or bilateral
Size	< 4 cm	Variable (3 cm)	> 4 cm	Variable
CT density	< 10 UH	> 10 UH	> 10 UH	> 10
Wash out cte	> 50%	< 50%	< 50 %	< 50%
MRI intensity **Signal drop**	T1 and T2 isointense Si	T2 hyperintensity	T1 and T2 hyperintensity No	T1 and T2 hyperintensity No
Necrosis or hemorrhage	Rare	Yes, vascularized, cystic	Yes	Yes
Growth over time (1 year) **Avidity 18 FDG PET/CT**	< 1cm No	0.5-1 cm Yes	> 2 cm Yes	1 cm Yes





Adaptado de E. Kebebew. Adrenal Incidentaloma. NEJM 2021, 384; 1542

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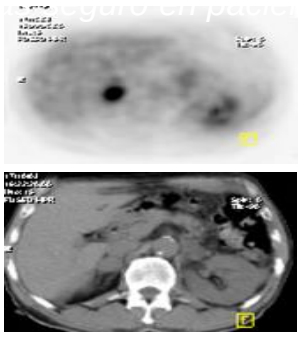
Metabolic Activity: PET-TC



- PET: FDG uptake by ↑ glucose utilization.
- CT: Morphology, S/C Density and Washout C/C.
- FP: 5% (infectious or inflammatory lesions, adenomas and cysts).
- FN: 1% (necrosis or hemorrhage and lesions < 1 cm).
- **Not useful for distinguishing pheochromocytoma from carcinoma or metastasis**

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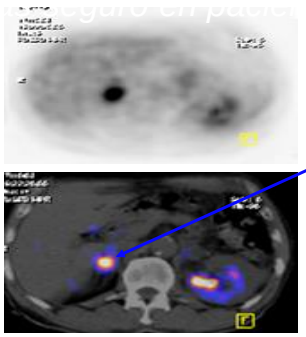
Metabolic Activity: PET-TC



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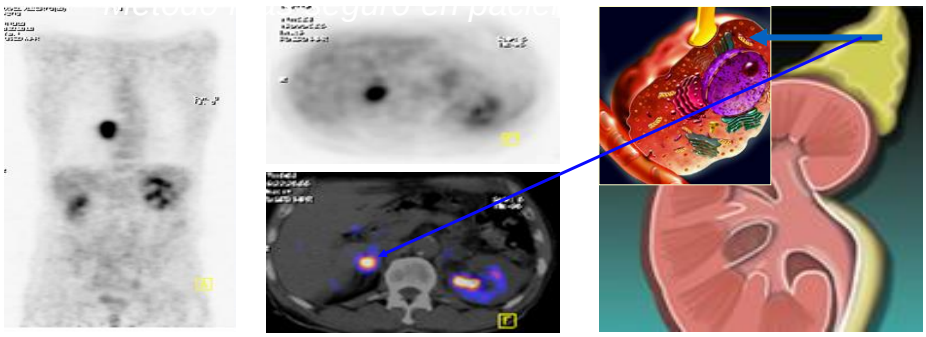

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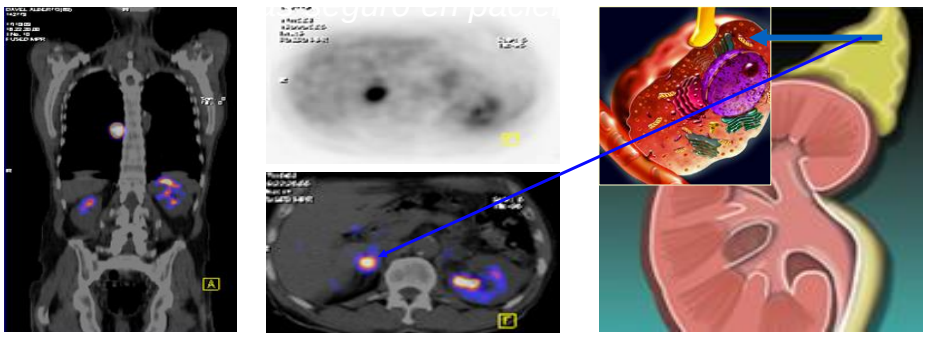

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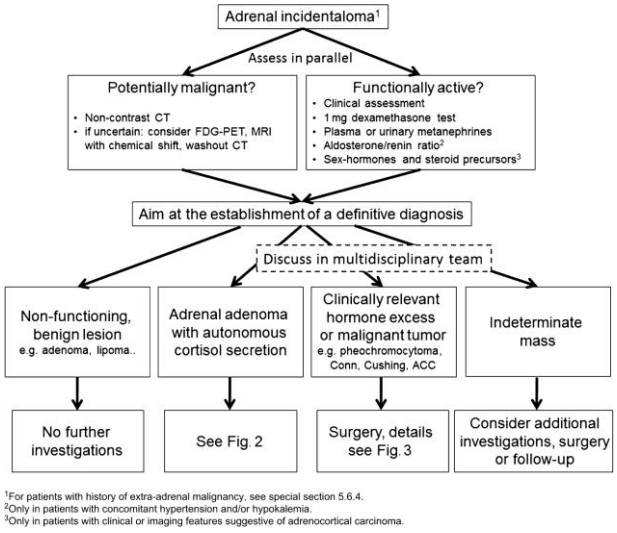
European Society Guidelines 2016



[1]For patients with history of extra-adrenal malignancy, see special section 5.6.4.
[2]Only in patients with concomitant hypertension and/or hypokalemia.
[3]Only in patients with clinical or imaging features suggestive of adrenocortical carcinoma.

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Adrenocortical Carcinoma. Size and Risk!

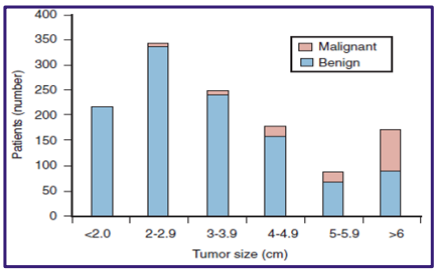
Extremely rare

4% of incidentalomas, observed in an Italian study with 1,004 patients

Functioning: cortisol secreting (Cushing's syndrome) and/or androgens (virilization in women)

Non-functioning

Characteristic radiological phenotype



Size and malignancy risk

Carcinoma de la Corteza Adrenal (CCA): Estudio multicéntrico de una serie de 40 pacientes de la Ciudad Autónoma de Buenos Aires

LEAL REYNA M[1*], CHERVÍN R[2], PARDES E[3], GÓMEZ RM[2(†)], LUPI SN[3], DE MIGUEL VC[4], MARTÍNEZ M[5], GARCÍA ML[6], TKATCH J[7], PAISSAN AL[4], ANGEL M[8], BELLI SH[7,8].

REV ARGENT ENDOCRINOL METAB. 2021; **58 #3**

28 % presentation as AI

Barzon et al. Eur J Endocrinol 2003; 149: 273-45
Mantero et al. A Survey Adrenal Incidentaloma JCEM 2000

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Biochemical Assessment

Pathology	Biochemistry	Conditions
Pheochromocytoma	**Fractionated metanephrines in 24 h urine**	All
Autonomous cortisol secretion (ACS)	**Nugent's test or dexamethasone suppression**	All
Hyperaldosteronism ***2%**	Aldosterone and renin	Arterial hypertension

Is It Hormonally Functional?

AACE/AAES Adrenal Incidentaloma Guidelines, Endocr Pract. 2009.
Fassnacht et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016;1

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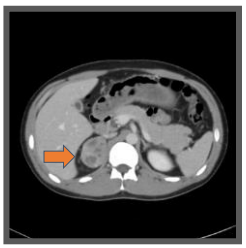
Pheochromocytoma



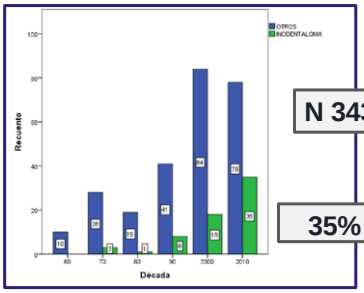
50% Diagnosis from AI

Fractionated Metanephrines 24 hs in Urine
S and E 98%

Characteristic Image Phenotype > 20 UH

Clinical Phenotype Medical History

< 10 UH in CT High Negative Predictive Value for Pheochromocytoma



N 343

35%

Canu L. et al. CT Characteristics of Pheochromocytoma: Prevalence for the Evaluation of Adrenal Incidentaloma. J. Clin. Endocrinol. Metab. 2019; 104, 312–318

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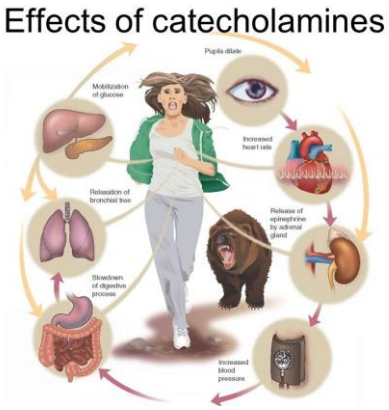
Clinical Presentation

- Episodic "spells" or paroxysms
  - Extremely variable in presentation- forceful heartbeat, pallor, tremor, headache, diaphoresis
  - May start with a sensation of a rush in the chest and sense of shortness of breath
  - Cold hands/feet
  - Increase sense of body heat and sweat occur towards the end of the spell
  - Can be spontaneous or precipitated by postural change, anxiety, exercise, etc
  - Occur multiple times daily or infrequently (monthly)



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Diagnosis

- Biochemical Assessment:
  - Plasma free metanephrines from supine patient using liquid chromatography with mass spec
  - Urine fractionated metanephrines by mass spec
    - Specificity of 91% and sensitivity of 97%
  - 24-hour urine fractionated metanephrines and catecholamines
  - >2-3-fold elevation is considered positive
  - Positive test results should receive confirmation- clonidine suppression test
- Medications that interfere with testing:
  - TCAs, decongestants, buspirone, cocaine, ethanol, amphetamines, Levodopa,

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Table 2. Characteristics of Pheochromocytoma-Associated Syndromes.*

Gene	Syndrome	Nonchromaffin Tumors	Transmission	Adrenal Tumors	Head and Neck Tumors	Extraadrenal Tumors†	Multiple Tumors	Metastatic Tumors‡	Family History§
						frequency (percent)			
VHL	VHL	Retinal and CNS hemangioblastomas, RCC, pancreatic neuroendocrine tumor, ELST	Autosomal dominant	>50	<1	10–24	>50	1–9	25–50
NF1	NF1	Cutaneous neurofibromas, malignant peripheral-nerve-sheath tumor, breast cancer	Autosomal dominant	>50	<1	1–9	25–50	1–9	10–24
RET	MEN-2	Medullary thyroid carcinoma, hyperparathyroidism	Autosomal dominant	>50	<1	<1	>50	<1	25–50
SDHA	PGL5	Rarely also pituitary adenoma, GIST, RCC	Autosomal dominant	25–50	25–50	25–50	1–9	1–9	1–9
SDHB	PGL4	Rarely also pituitary adenoma, GIST, RCC	Autosomal dominant	25–50	25–50	25–50	10–24	25–50	10–24
SDHC	PGL3	Rarely also pituitary adenoma, GIST	Autosomal dominant	1–9	>50	<1	10–24	Not reported	10–24
SDHD	PGL1	Rarely also pituitary adenoma, GIST, RCC	Autosomal dominant, maternal imprinting	10–24	>50	10–24	>50	1–9	25–50
SDHAF2	PGL2		Autosomal dominant, maternal imprinting	1–9	>50	Not reported	>50	Not reported	>50
MAX	No name	Rarely also RCC	Autosomal dominant	>50	<1	1–9	>50	1–9	25–50
TMEM127	No name		Autosomal dominant	>50	1–9	<1	25–50	10–24	1–9

* For multiple endocrine neoplasia type 2 (MEN-2), von Hippel–Lindau disease (VHL), and neurofibromatosis type 1 (NF1), the frequencies of the characteristics shown are for patients with chromaffin tumors, since such tumors do not develop in all patients with these syndromes. CNS denotes central nervous system, ELST endolymphatic-sac tumor of inner ear, GIST gastrointestinal stromal tumor, HPT hyperparathyroidism, PGL paraganglioma syndrome (PGL1 through PGL5 denote paraganglioma syndromes 1 through 5), and RCC renal-cell carcinoma.
† These tumors consist of retroperitoneal, pelvic, and thoracic tumors.
‡ These tumors consist of metastatic pheochromocytoma and paraganglioma.
§ Shown is the frequency of a family history of components of the given syndrome.

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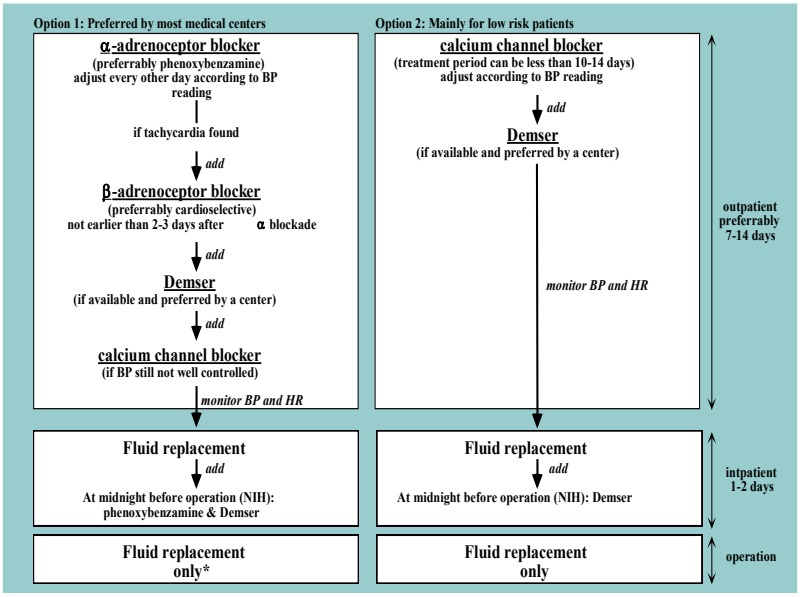
Treatment: Surgery



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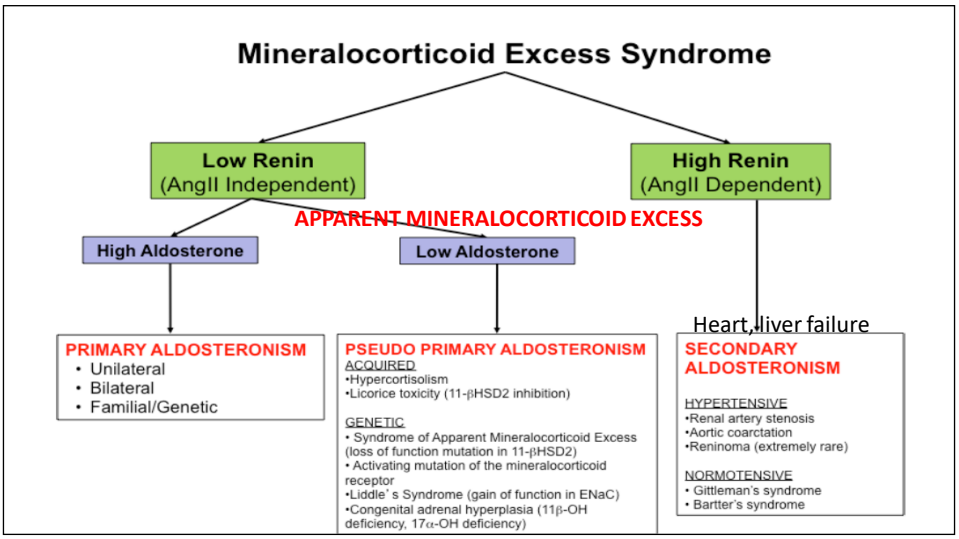
Primary Hyperaldosteronism



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Epidemiology

- 10-20% of all pts with HTN
- 40% of pts with resistant HTN
- Mostly diagnosed in 3rd-6th decades
- Patients with PA have 4-12 fold higher rates of MI, stroke, CAD, and arrythmias that people with primary HTN, <u>independent of blood pressure</u>[†]
- 3 recent studies have shown that we are not testing patients for PA.
  - In each study, only ~2% of patients with resistant HTN were screened for PA[†‡β]

* Funder JW, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. JCEM. 2016
† Jaffe G, et al. Screening rate for primary aldosteronism in resistant hypertension. Hypertension. 2020.
‡ Ruhle BC, et al. Keeping primary aldosteronism in mind: deficiencies in screening at-risk hypertensives. Surgery. 2019.
B BrownJM, et al. The unrecognized prevalence of primary aldosteronism. Ann Intern Med. 2020.

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Clinical Features

Hypertension

- Hypervolemia due to sodium and water retention→ increased systemic vascular resistance
- Suppression of plasma renin

Hypokalemia

- Metabolic alkalosis
- Muscle cramps
- Fatigue

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Testing for Primary Aldosteronism

Suspicious for Primary Aldosteronism
- HTN+ with↓K, resistant HTN, adrenal incidentaloma with HTN

↓

Case Detection Test: Morning blood sample in seated ambulant patient
- Plasma aldosterone concentration (PAC)
- Plasma renin activity (PRA) or plasma renin concentration (PRC)

↓

PAC ≥ 12 ng/dL
and
↓ PRA (<1.0ng/mL/hr) or ↓ PRC (< lower limit of reference range)

↓

Confirmatory Testing

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Confirmatory Testing

TEST	METHOD	CUT-OFFS	PRECAUTIONS
ORAL SALT LOADING	Salt load 6g/day for 3 days with adequate K+	Day 4, 24 hr urine aldosterone > 12 mcg, urine Na >200 mmol	Avoid in renal failure, CHF, uncontrolled HTN
SALINE SUPPRESSION TEST	2L normal saline infused over 4 hours (seated/recumbent)	Post-saline Aldosterone >10ng/dl	Avoid in renal failure, CHF, uncontrolled HTN
FLUDROCORTISONE SUPPRESSION TEST	Fludrocortisone 0.1 mg every 6 hrs, K+ tabs every 6 hrs, Na 30 mmol tid qac for 4 days	Day 4 , 10 am aldosterone >6 ng/dl	Cumbersome, not much experience
CAPTOPRIL CHALLENGE TEST	Captopril 25-50 mg once	Aldosterone at 0,1 or 2h Suppression of aldosterone <30%	Substantial False negatives

Formal confirmatory testing for PA is not needed in pt <35yo with HTN, spontaneous hypokalemia, PAC > 15, and suppressed PRA or PRC.

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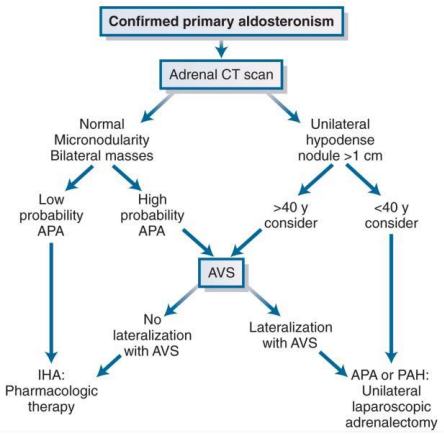
Post Diagnosis Management of PA

Imaging

- CT adrenal protocol
- MRI is not superior

Consults

- Endocrinology
  - Will determine with pt whether to medically manage versus workup for surgery.



APA= Aldosterone-producing adenoma
AVS= Adrenal vein sampling
IHA= idiopathic hyperaldosteronism
PAH= primary adrenal hyperplasia

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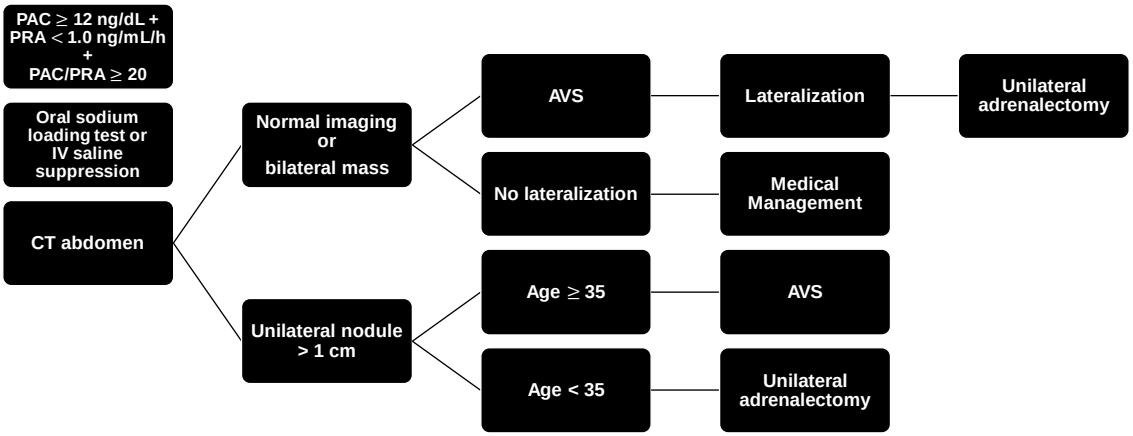
Summary



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Treatment

- Unilateral Adrenalectomy (ALDOSTERONOMA)
- Medical Treatment (BILATERAL HYPERPLASIA)
  - Mineralocorticoid Receptor Antagonists
    - Spironolactone
    - Eplerenone
  - Sodium Channel Antagonists
    - Triamterene
    - Amiloride

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Mild Autonomous Cortisol Secretion (ACS)

Subclinical Cushing's syndrome
Subclinical hypercortisolism

Autonomous Cortisol Secretion

Mild Autonomous Cortisol Secretion (MACS)

MACS
10- 46 %
AI

2% general population

Delivanis et al. Modern Management of Mild Cortisol Autonomous Secretion. CLINICAL PHARMACOLOGY & THERAPEUTICS. 2019

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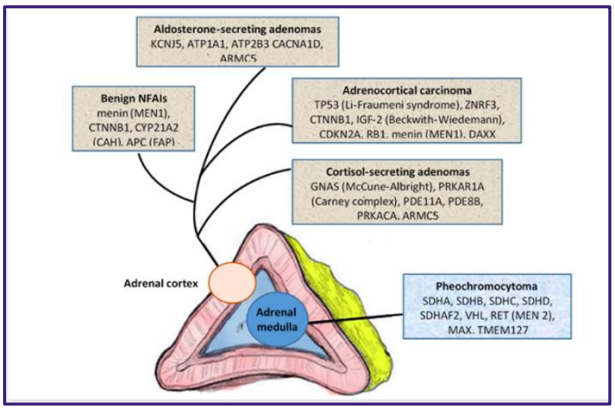
Pathophysiology

AI:
Spectrum of different pathologies that share the same discovery pathway



Different genetic causes and pathophysiological mechanisms. Not well known in NF Adenomas

Hypothesis

Aging/ischemia

Insulin resistance

Alterations in HPA axis feedback sensitivity

Adrenal Diseases. Endotext 2021

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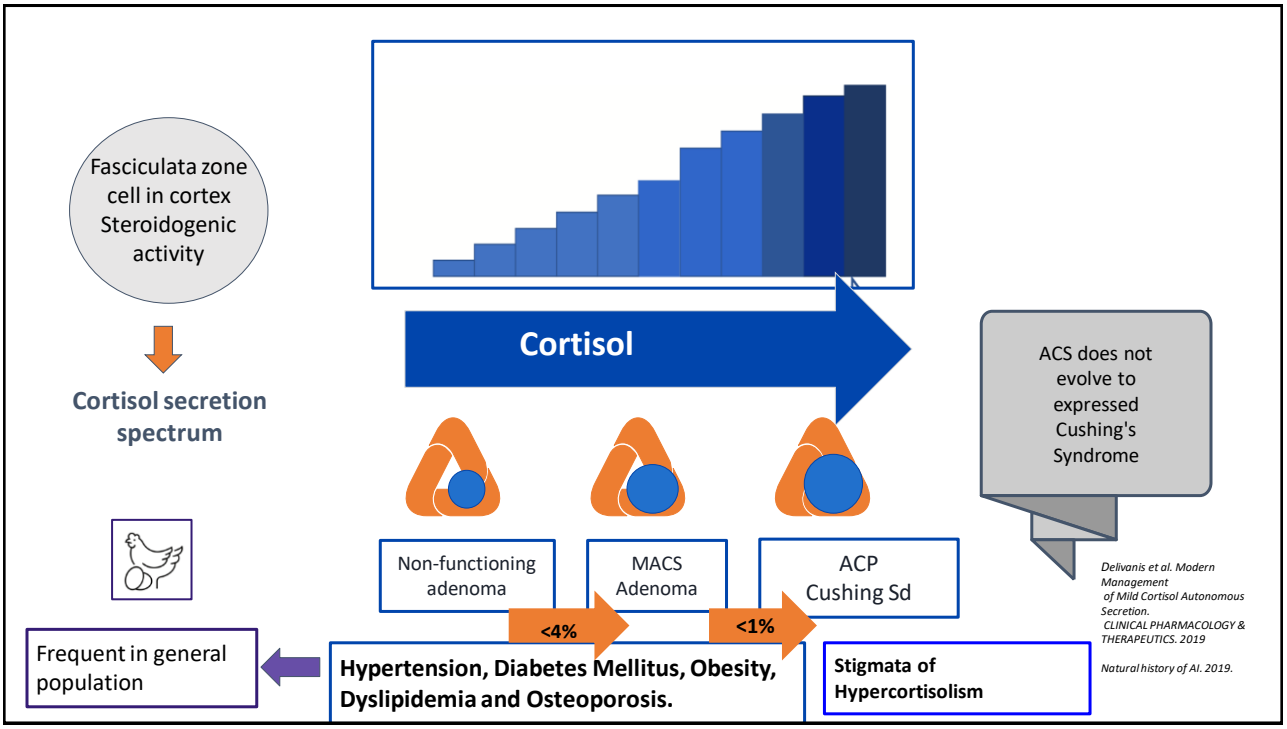

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Autonomous Cortisol Secretion Diagnosis

Inhibition Test with 1 mg dexamethasone (Nugent Test)

- **5 mcg/dl confirmed CS**
  Clinically significant value (NIH 2003, Endocrine Society 2008)
- **1.8-5 mcg/dl (ESE/ENSAT, AACE) Mild ACS**

Confirm ACTH independence

Test	Non Cortisol secretion	Mild ACS	CS
Nugent	< 1.8 mcg/dl	1.8 - 5 mcg/dl	> 5 mcg/dl
UFC	Normal	Normal	Normal/high
LN Salivary Cortisol	Normal	Normal	Normal/high
ACTH	Normal	Normal low	Inhibited
DHEAS	Normal	Normal low	Inhibited

Consider drugs involved in cytochrome P450 and estrogens.

NIH State-of-the-Science Conference on Management of the Clinically Inapparent Adrenal Mass ("Incidentaloma")

Delivanis et al. Modern Management of Mild Cortisol Autonomous Secretion. CLINICAL PHARMACOLOGY & THERAPEUTICS. 2019

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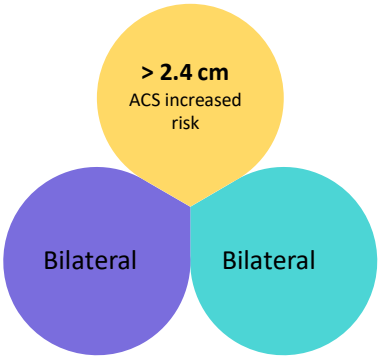
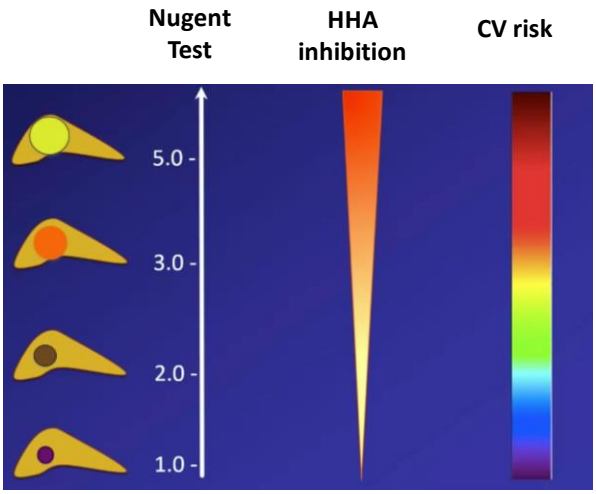
Larger Size, Bilateral, ACS Increased Risk





Adrenal Incidentaloma.
M. Terzolo
Meet the Professor.
ENDO 2017

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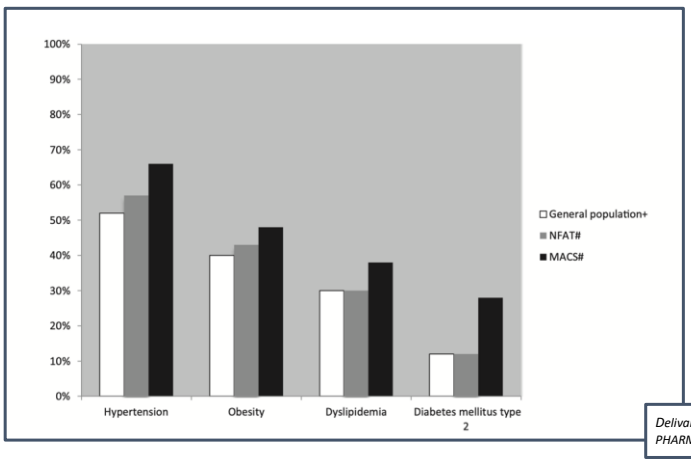
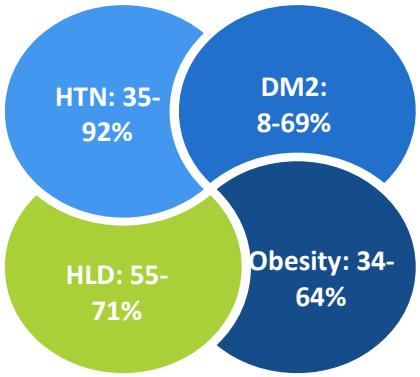
MACS Clinical Consequences

Increased Cardiovascular Risk (Hypertension, Obesity, Dyslipidemia, Type 2 Diabetes Mellitus), Cardiovascular Events, Osteopenia, Osteoporosis and Fractures.



Prevalence



Delivanis et al. Modern Management of Mild Cortisol Autonomous Secretion. CLINICAL PHARMACOLOGY & THERAPEUTICS. 2019

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MACS Clinical Consequences

Prevalence of vertebral fracture
46-82%
decreased risk post adrenalectomy

CV disease prevalence
(similar to expressed CS):
→ **Increased carotid artery intima-media thickness and plaques.**
→ **Diastolic dysfunction**
→ **Increased arterial stiffness**

Increased **mortality in 1 mg DST > 5 mcg/dl** compared to **1.8-5 mcg/dl**

Delivanis et al. Modern Management of Mild Cortisol Autonomous Secretion. CLINICAL PHARMACOLOGY & THERAPEUTICS. 2019

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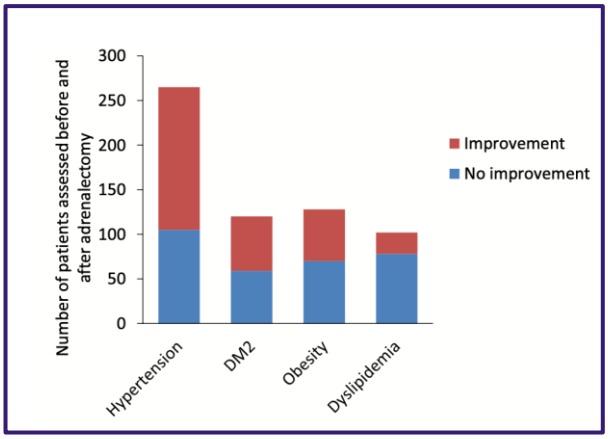
THERAPY OF ENDOCRINE DISEASE

Improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and subclinical Cushing's syndrome: a systematic review and meta-analysis

Irina Bancos[1], Fares Alahdab[2], Rachel K Crowley[3], Vasileios Chortis[4,5], Danae A Delivanis[1], Dana Erickson[1], Neena Natt[1], Massimo Terzolo[6], Wiebke Arlt[4,5], William F Young Jr[1] and M Hassan Murad[2]



Improvement of Cardiovascular Risk Factors in Adrenalectomy vs. No Adrenalectomy.

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Pseudo-Cushing's Syndrome

- Conditions in which a patient presents clinical characteristics suggesting a true Cushing's syndrome and with some biochemical evidence of hypercortisolemia
- Both settle after resolution of the predisposing condition
- Depression and alcohol abuse are the two most common causes

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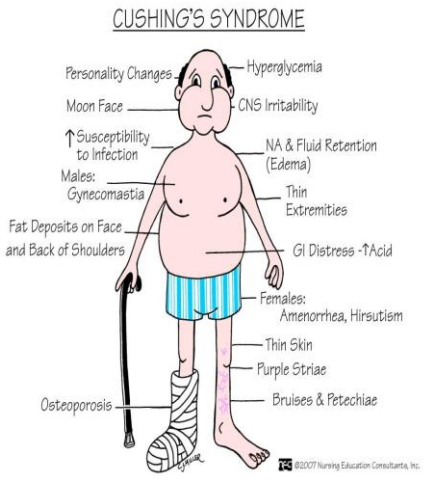
Hypercortisolism



- Hypokalemic metabolic alkalosis (d/t mineralocorticoid action of cortisol in the renal tubules)
- Insulin resistance and hyperinsulinemia. Glucose intolerance 20%-30%, DM 30%-40%
- Increased total and TG cholesterol (increased hepatic VLDL synthesis)
- Increased CVD events, increased carotid artery intima-media thickness and atherosclerotic plaques
- HTA
- Increased risk of TEB (increases clotting factors, including factor VIII, fibrinogen, and von Willebrand factor, and reduces fibrinolytic activity)
- Ophthalmic complications include glaucoma and exophthalmos
- Psychiatric symptoms such as insomnia, depression, anxiety, easy irritability, paranoid episodes and attempted suicide or panic attacks

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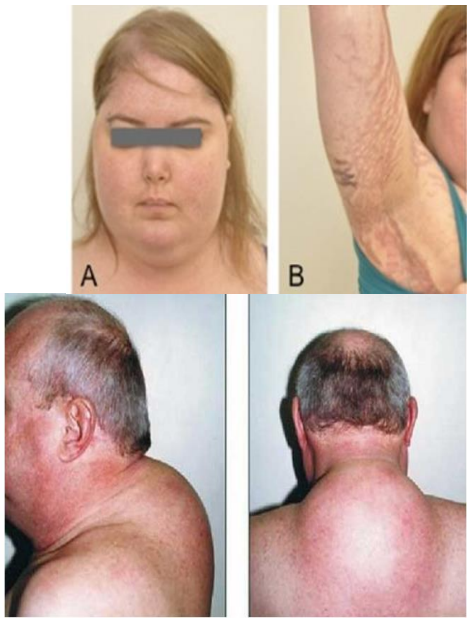

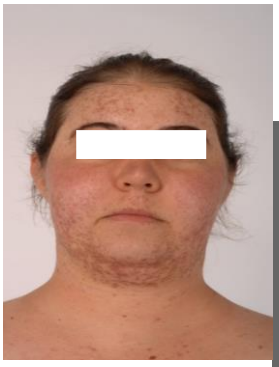

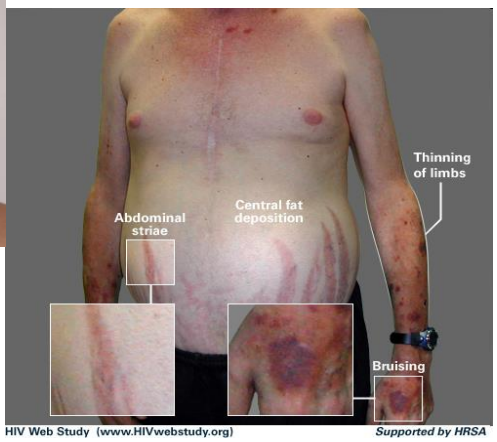

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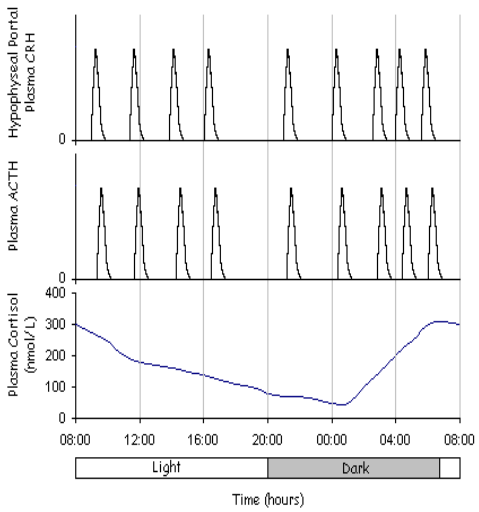
Biochemical Diagnosis of Cushing's Syndrome

- Circadian Rhythm - Diurnal
- Total serum cortisol is very challenging and unreliable
  - Oral contraceptives and some medical conditions will increase cortisol-binding globulin and therefore total cortisol
- Time difference adjustment
- Patient resting in bed

OTHER EVIDENCE



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Free Urine Cortisol
(Normal Range 10-100 mcg/24 Hours)

- **Pros:**
  - Non-invasive
  - Not influenced by diurnal rhythm.
  - Non-affected by increased levels of CBG (cortisol-binding proteins)
- **Cons:**
  - Intensive labor for patients (urine collection)
  - Can not be used in patients with renal failure or dialysis
  - High rate of cross reactivity
  - Most urine assays collect cortisol metabolites (95%); only 2-3 % of free cortisol

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Late Night Salivary Cortisol
Sensitivity: 92% , Specificity: 96%

- **Pros:**
  - Non-invasive: can be used in infants, children, patients with venous insufficiency, etc
  - Avoid secretion increase induced by stress (as with a blood draw)
  - No need to freeze or keep refrigerated
  - Provides a measure of free cortisol
  - Correlates well with serum levels over a 24-hour period
- **Cons:**
  - Provides measurement of cortisol concentration at a single point in time
  - Periodontal disease, diet, toothbrushing can affect the results
  - The amount of sample may be low (e.g., dry mouth, impatient person)

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Nugent or 1-mg Dexamethasone Suppression Test

- Dexamethasone 1 mg at 23:30 or midnight
- Fasting plasma cortisol the next day at 8-9 AM
- False positive results
  - increase in CBG (estrogens)
  - 25% of women on OCP are false-positive
  - increased metabolism of dexamethasone (anticonvulsant drugs)
- False-negative results
  - reduced dexamethasone clearance in hepatic or renal insufficiency
- **THE BEST TEST FOR ADRENAL CUSHING'S DISEASE**

Drugs
Drugs that accelerate dexamethasone metabolism by induction of CYP 3A4
Phenobarbital
Phenytoin
Carbamazepine
Primidone
Rifampin
Rifapentine
Ethosuximide
Pioglitazone
Drugs that impair dexamethasone metabolism by inhibition of CYP 3A4
Aprepitant/fosaprepitant
Itraconazole
Ritonavir
Fluoxetine
Diltiazem
Cimetidine

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Guidelines Recommendations

Who should get tested?

We recommend testing for Cushing's syndrome in the following groups:

- Patients with unusual characteristics for their age (e.g., osteoporosis, hypertension, hypertension, etc.)
- Patients with multiple, progressive characteristics, particularly those most predictive of Cushing's syndrome
- Children with height decreasing percentile and weight gain
- Patients with adrenal incidentaloma compatible with adenoma

Initial tests

We recommend the following tests based on their suitability for a given patient:

- Urine free cortisol (UFC; at least two measurements)
- Nocturnal salivary cortisol (two measurements)
- Dexamethasone suppression test (DST) of 1 mg at overnight

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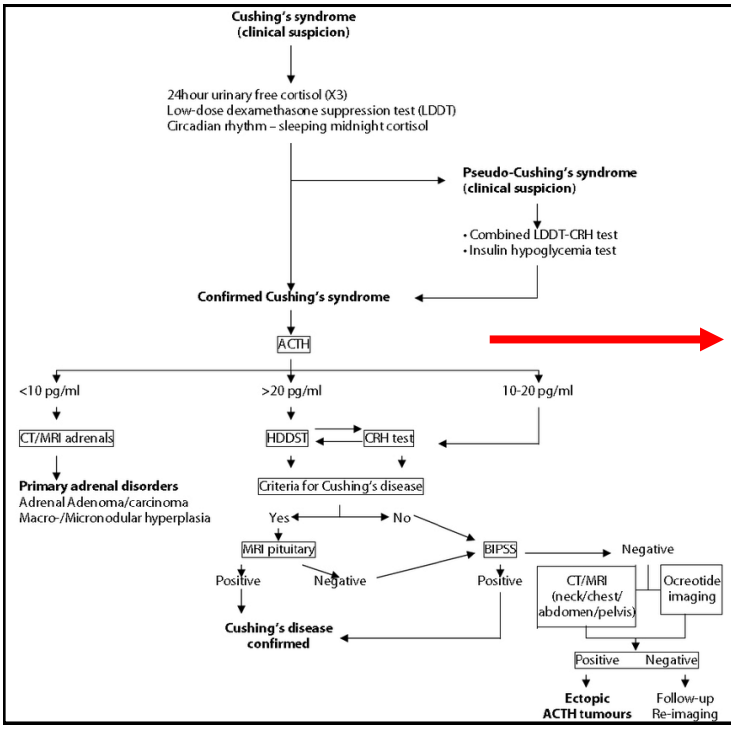
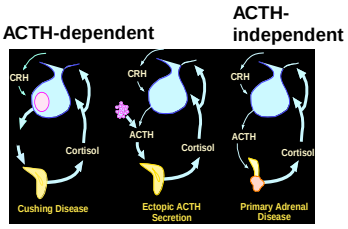


Plasma ACTH Measurement

< 10 pg/ml
ACTH-independent

> 20 pg/mL
ACTH-dependent
Higher in ectopic Cushing's disease

5 - 20 pg/ml
Undetermined



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Bilateral Adrenal Incidentaloma

- Bilateral lesions may represent co-occurrence of different entities. Each lesion should be evaluated separately following the recommendations for unilateral lesions.
- **CS** is **more frequent** in bilateral incidentaloma (BI) than in unilateral adrenal incidentaloma (UAI)
- Prospective study with 298 patients (224 UAI and 74 BI):
- → **ACS: 35% IAB vs 17% IAU**

- The same evaluation is recommended as for UAI and the same considerations for comorbidities
- Perform 17 OH Progesterone dosage to rule out CAH

Evaluate adrenal insufficiency in case of infiltration, metastasis or hemorrhage.

Young WF Jr. Management approaches to adrenal incidentalomas. A view from Rochester, Minnesota. Endocrinol Metab Clin North Am. 2000; Fassnacht et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016;1

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When to Prescribe Surgery?
Laparoscopic Adrenalectomy

Pheochromocytoma: ALWAYS
(Pre alpha-beta blocking preparation Cx)

Adrenocortical Carcinoma: ALWAYS
(Open surgery)
Hyperaldosteronism: SELECTED

Cushing's Syndrome: ALWAYS
MACS Selected Cases

Non-adenomatous Image **phenotype** **Consider Cx**

Metastases in selected cases

Fassnacht et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016

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Treatment Individualization

MACS
Nugent 1.8- 5 mcg/dl
+
Comorbidities

Individual approach, **medical treatment and follow-up vs. considering Cx**

Post-operative corticosteroids

50% Adrenal Insufficiency

- ★ Age
- ★ Comorbidities
- ★ Patient preference
- ★ Tumor size (>2.4cm)

Bilateral
Gland of unilateral adrenalectomy of > size

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Medical Therapy

- When surgery is delayed, contraindicated or unsuccessful
- Preoperative: to reverse hypercortisolemia and reduce complications
- Cushing's disease while waiting for pituitary radiotherapy to take effect
- In occult ectopic ACTH syndrome: pending reinvestigation
- Palliative modality in patients with metastatic disease that is causing Cushing's syndrome

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Steroidogenesis Inhibitors

Cortisol

Ketoconazole/Levo/etomidate
Metyrapone
Mitotane
Etomidate
Osilodrostat

Drugs that decrease ACTH secretion:
Octreotide, Paseriotide, Cabergoline, Bromocriptine

Glucocorticoid antagonist: Mifepristone

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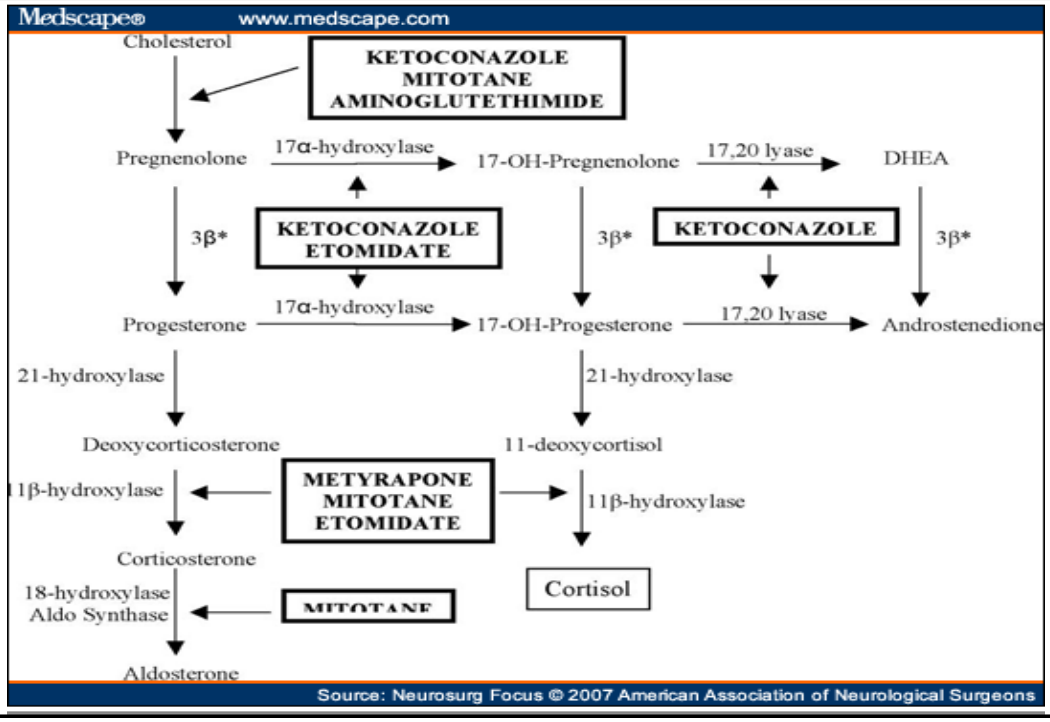

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Which Medication?

Drug	Pros	Cons
Ketoconazole	Fast	SE: GI, LFTs (death) Needs stomach acid Interactions with other drugs (CYP3A4 substrate)
Metyrapone	Fast	SE: GI, hirsutism, acne, HTN, neutropenia rarely, hard to obtain
Mitotane	Effective	Takes time to be effective Can't track serum cortisol levels SE: GI, neurology, ↓WBC, teratogenic
Etomidate	Fast, IV → can't be taken oral	Must start in the ICU Temporary measure
Paseriotide	Effective	Injectable, may worsen/cause DM
Mifepristone	FDA approved	Can't follow serum cortisol levels Anti-progestin (abortifacient, vaginal bleeding), hypokalemia

Treatment goal: UFC in normal range
Serum cortisol 6-12 mcg/dl (before AM drugs)

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AI Follow-up

NIH 2002

- Repeat images 6-12 months. If there are not change: STOP
- Repeat annual hormonal studies for 4 years

ESE 2016

- Lesions < 4 cm and < 10 HU: NO further imaging
- NON-functioning adenomas: NO repeat biochemistry
- Indeterminate imaging: surgery or repeat at 6-12 months (imaging modality can be changed). If growth >20% is recommended Cx

Fassnacht et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016

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Conclusions

- AI is a common endocrine diagnosis
- Most patients can be reassured and discharged
- NFAT that have an attenuation of 10 Hounsfield units or less on CT and that are smaller than 4 cm in greatest diameter generally do not warrant intervention or long-term follow-up
- MACS is a challenging diagnosis and treatment should be individualized and focused on comorbidities
- Patients with pheochromocytoma should undergo adrenalectomy after adequate presurgical alpha-blockade and beta-blockade, if necessary.
- Cushing's Syndrome must be diagnosed and treated in time
- Prospects for new radiological and urinary biomarkers will improve diagnostics in the coming years

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