Essential in Endocrinology

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Key Long Case

- History
- Physical examination
- Laboratory investigation
  - Interpretation: CT abdomen, CT brain, etc. Level 1 & 2
  - Clinical correlation
- Diagnosis
- Treatment
  - Specific
  - Supportive
- Advice

Level 2

Imaging

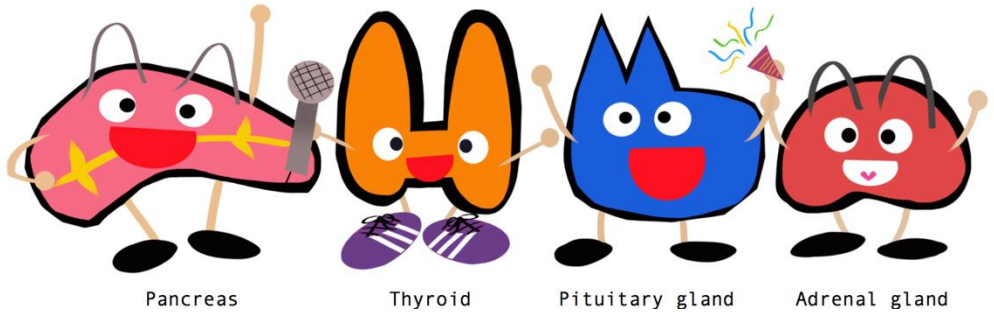
- Bone and joint radiography, Chest X-ray
- Skull X-ray
- CT brain, abdomen, thorax
- MRI brain
- Thyroid uptake and scan

Hormones

- Adrenal function test
- Parathyroid hormone
- Pituitary function test
- Thyroid function test
- Urinary metanephrine/normetanephrine
- Water deprivation test
- Reproductive hormones

Outlines

- Adrenal insufficiency
  - Primary adrenal insufficiency
  - Central adrenal insufficiency
- Hypopituitarism
  - Anterior pituitary/posterior pituitary
- Functioning pituitary tumor
  - Cushing's disease
  - Prolactinoma
  - Acromegaly
- Aldosterone
  - Primary aldosteronism
  - Secondary aldosteronism
- Cushing's syndrome
  - Exogenous Cushing's
  - Endogenous Cushing's
    - ACTH-dependent Cushing's syndrome
    - ACTH-independent Cushing's syndrome
- Pheochromocytoma
  - Syndromic PPGL
- Hyperthyroidism
- Hypercalcemia
  - PTH-dependent hypercalcemia
  - PTH-independent hypercalcemia
- MEN1
- Hypoglycemia



Adrenal Insufficiency

Adrenal Insufficiency: Manifestations

- Manifest with symptoms of **chronic adrenal insufficiency**
  - Non-specific symptoms, e.g., nausea/vomiting, weight loss, postural hypotension, etc.

- Some patients may present with **adrenal crisis**.
- Decompensated stage of adrenal insufficiency
  - Always look for *precipitating factors*, e.g., infections, drug interactions, etc.
    - **OR** it can be the first manifestation of chronic adrenal insufficiency in some patients.

Adrenal Insufficiency: Signs and Symptoms

Symptoms

- Fatigue or anorexia
- GI symptoms
- Salt craving หิวเกลือ* Mineralocorticoid deficiency
- Postural hypotension

Signs

- Weight loss
- Fever ไม่จำเป็น
- Hyperpigmentation* ผิวคล้ำขึ้น ↑ ACTH levels
- Hypotension (SBP<110 mmHg)

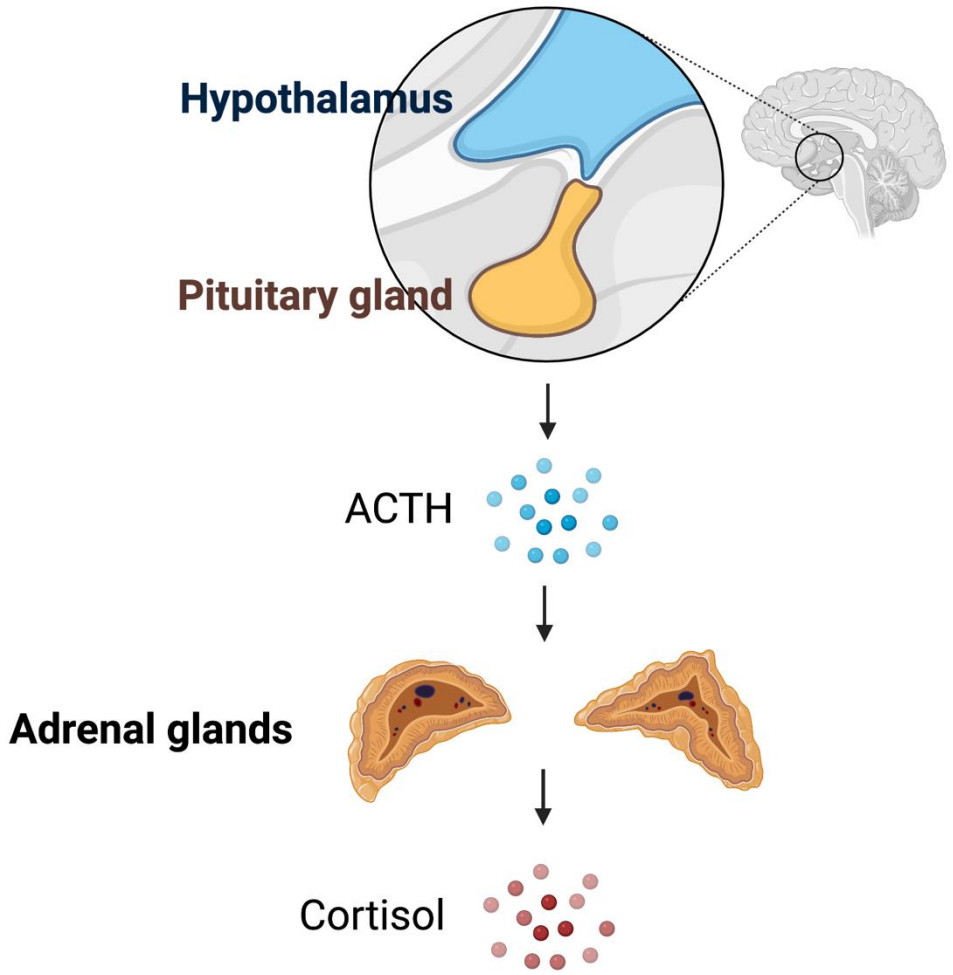
*Only found in primary adrenal insufficiency

Laboratory Findings

- Electrolyte disturbances: most common
  - Hyponatremia
  - Hyperkalemia (in primary adrenal insufficiency)
  - Hypercalcemia
- Azotemia
- Anemia
- Eosinophilia

Pathophysiology of Adrenal Insufficiency

Hypothalamic-pituitary-adrenal axis



Central adrenal insufficiency

- May be called secondary and tertiary adrenal insufficiency

Patients may have other hypothalamic/pituitary hormone deficits.

- e.g., TSH, FSH/LH, vasopressin

Primary adrenal insufficiency

Patients may have other adrenal hormone deficits.

- Mineralocorticoids (including aldosterone)
- Adrenal androgen

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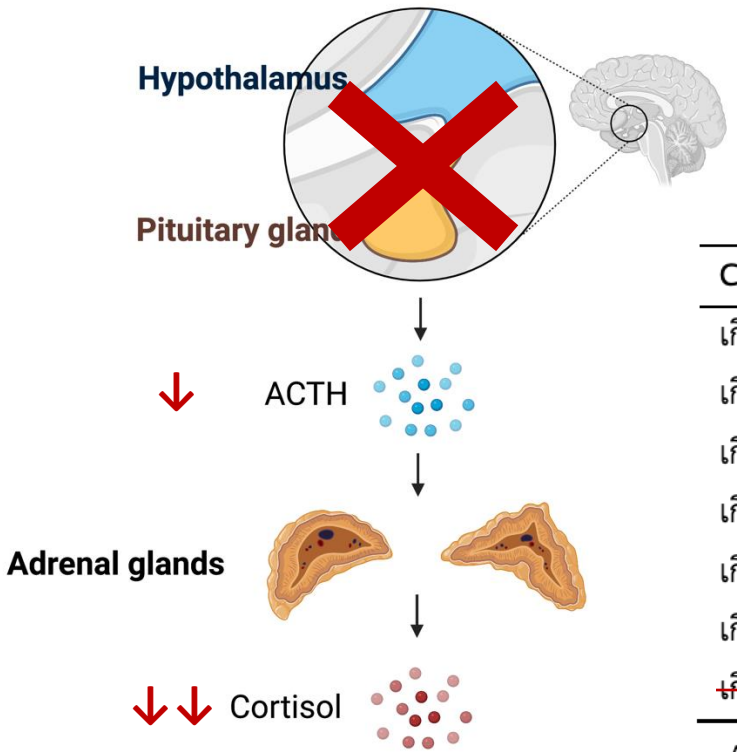
Etiology of Adrenal Insufficiency



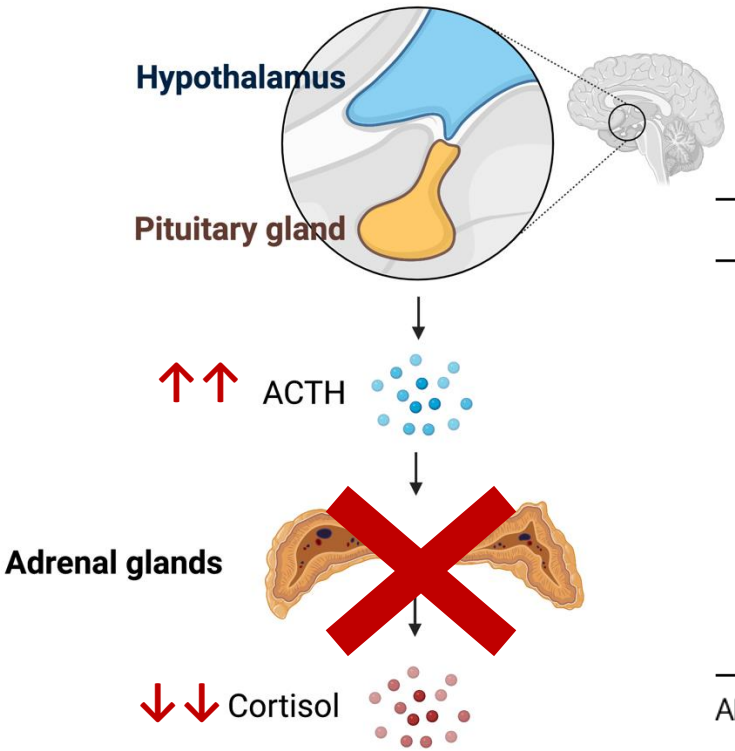
& PD1, PDL1 inhibitors
Immune checkpoint inhibitors can also result in primary adrenal insufficiency.

Central Adrenal Insufficiency
เกิดจากการใช้ยาบางชนิด (glucocorticoids, opiates, CTLA-4 blockers)
เกิดจากเนื้องอกบริเวณต่อมใต้สมองและไฮโปทาลามัส
เกิดตามหลังการรักษาเนื้องอกบริเวณต่อมใต้สมองและบริเวณข้างเคียง (ผ่าตัดหรือฉายแสง)
เกิดจากการขาดเลือดบริเวณต่อมใต้สมอง (pituitary apoplexy, Sheehan's syndrome)
เกิดจากการลุกลามของมะเร็งไปบริเวณต่อมใต้สมอง
เกิดจากการอักเสบหรือติดเชื้อบริเวณต่อมใต้สมอง
~~เกิดจากสาเหตุทางพันธุกรรม (isolated ACTH deficiency หรือ combined pituitary hormone deficiencies)~~

APS, autoimmune polyendocrine syndrome; CAH, congenital adrenal hyperplasia; AHC, adrenal hypoplasia congenita; ALD, adrenoleukodystrophy; CTLA-4, cytotoxic T-lymphocyte-associated protein 4

วาสิตา วราชิต ภาคสุข. "Adrenal insufficiency" Inpatient medical consultation การรับปรึกษาผู้ป่วยในทางอายุรศาสตร์. พิมพ์ครั้งที่ 1. กรุงเทพมหานคร

Etiology of Adrenal Insufficiency



Primary Adrenal Insufficiency
เกิดจากการติดเชื้อบริเวณต่อมหมวกไต
เกิดจากภาวะออโตอิมมูน (isolated, APS type I, APS type II)
เกิดจากการลุกลามของมะเร็งไปที่ต่อมหมวกไต (metastatic tumor)
เกิดจากภาวะเลือดออกที่ต่อมหมวกไต (adrenal hemorrhage)
เกิดจากสาเหตุทางพันธุกรรม เช่น CAH, AHC, ALD และ FGD เป็นต้น
เกิดตามหลังการผ่าตัดต่อมหมวกไตสองข้าง (bilateral adrenalectomy)
เกิดจากการใช้ยาบางชนิด

APS, autoimmune polyendocrine syndrome; CAH, congenital adrenal hyperplasia; AHC, adrenal hypoplasia congenita; ALD, adrenoleukodystrophy; CTLA-4, cytotoxic T-lymphocyte-associated protein 4

Patients may have other adrenal hormone deficiencies.

↓ Aldosterone

↓ Adrenal androgen

วาสิตา วราชิต ภาคสุข. “Adrenal insufficiency” Inpatient medical consultation การรับปรึกษาผู้ป่วยในทางอายุรศาสตร์. พิมพ์ครั้งที่ 1. กรุงเทพมหานคร

History Taking

- ซักเรื่องอาการของ adrenal insufficiency
  - เบื่ออาหาร น้ำหนักลด ไข้ น้ำตาลต่ำ (หรือน้ำตาลคุมได้ดีขึ้นในคนที่เป็นเบาหวานเดิมทั้งที่ใช้ยาเท่าเดิม หรือ น้ำตาลตกทั้งที่เดิมไม่เคยเป็น) ลุกนั่งเปลี่ยนท่าทางแล้วมีอาการหน้ามืด ฯลฯ

- ซักหา etiology ของ adrenal insufficiency

History Taking

ซักเพื่อหา etiology (central adrenal insufficiency)

- Drug-induced
  - Glucocorticoids ถาม dose duration, Cushingoid feature, ประวัติน้ำหนักขึ้น หน้ากลมขึ้น เคยหยุดแล้วมีอาการอ่อนเพลีย
  - Immune checkpoint inhibitor ถามประวัติมะเร็ง ประวัติยาที่ใช้ และ onset

- Hypothalamic and pituitary tumors
  - Pituitary adenoma ถามเรื่อง mass symptoms, อาการ hormonal deficiency อื่นๆ, อาการของ functioning tumors อื่นๆ, ไม่ควรมี AVP deficiency ยกเว้น postoperative อาจมีได้
  - Craniopharyngioma เกิดได้ตั้งแต่อายุน้อย อาจมี AVP deficiency ร่วมด้วยได้

- Sheehan syndrome ประวัติตกเลือดหลังคลอด ไม่มีน้ำนมให้ลูกกิน หลังจากคลอดบุตรอาจจะไม่มีประจำเดือน
- Pituitary apoplexy ประวัติ thunderclap headache
- Metastatic cancer เด่นเรื่อง AVP deficiency

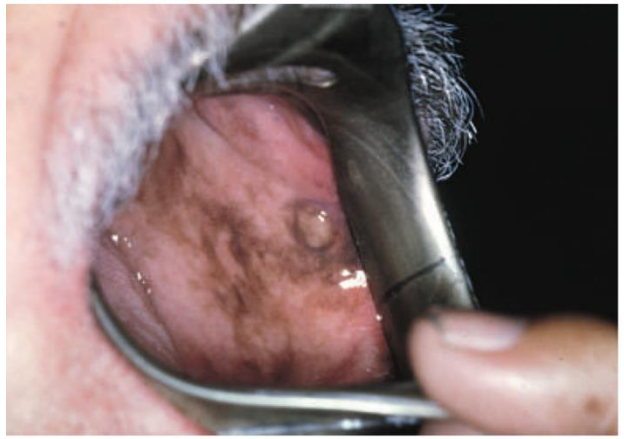
History Taking

ซักเพื่อหา etiology (ต่อ – primary adrenal insufficiency)

- อาการหิวเกลือ (mineralocorticoid deficiency), ผิวคล้ำขึ้น (elevated ACTH)
- Onset หากเป็นตั้งแต่เด็ก 👶👧 คิดถึงโรคทางพันธุกรรม
  - Most common = CAH ถ้าจะออกสอบบอร์ด น่าจะ 21-OH deficiency ที่เป็น classic salt-wasting form ผู้ป่วยจะมาด้วย ambiguous genitalia + adrenal crisis ตั้งแต่เด็ก
  - Adrenoleukodystrophy (ALD): presenting symptoms are usually AI in infants (80%) and myelopathy in adults
- Infection:
  - ***Non-HIV, non-DM มองหา Adrenal histoplasmosis หรือ Adrenal TB ด้วย!!!***
  - HIV + low CD4 มองหา opportunistic infection ต่าง ๆ
- Infiltration:
  - Metastatic CA: CA metastasis ≠ primary AI เพราะ adrenal gland ต้องเสียมากและสองข้าง จึงจะมีอาการของ primary AI
- Adrenal hemorrhage
  - *มักมาด้วย **acute AI + ปวดท้อง + มี risk factors***
    - Risk factors: coagulopathy (on anticoagulants, antiphospholipid syndrome), trauma, sepsis
- Other autoimmune diseases, e.g., autoimmune polyendocrine syndrome (APS)
  - APS type 1: primary AI + chronic mucocutaneous candidiasis + hypoparathyroidism
  - APS type 2: primary AI + autoimmune thyroid disease และ/หรือ T1DM

แนวทางการตรวจร่างกาย

- Vital signs: hypotension, postural hypotension, tachycardia
- Local tumor effect: VF defect ในกลุ่ม pituitary tumor ที่ compress optic chiasm
- Skin hyperpigmentation ใน primary AI: บริเวณที่พบเช่น palmar crease, knuckle, buccal mucosa และ surgical scar
- Signs ของ autoimmune disease อื่น เช่น anemia (B12 deficiency), thyroid abnormalities, vitiligo, mucocutaneous candidiasis



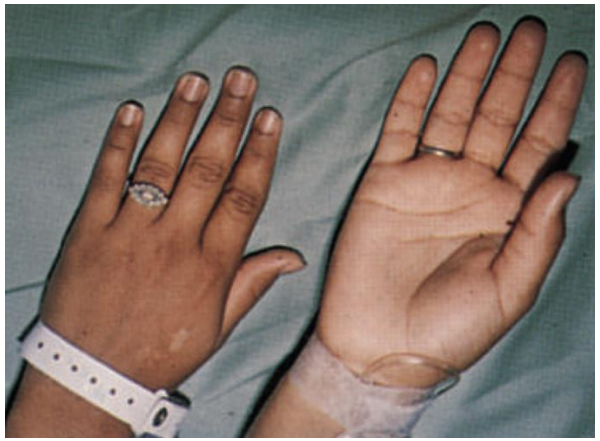
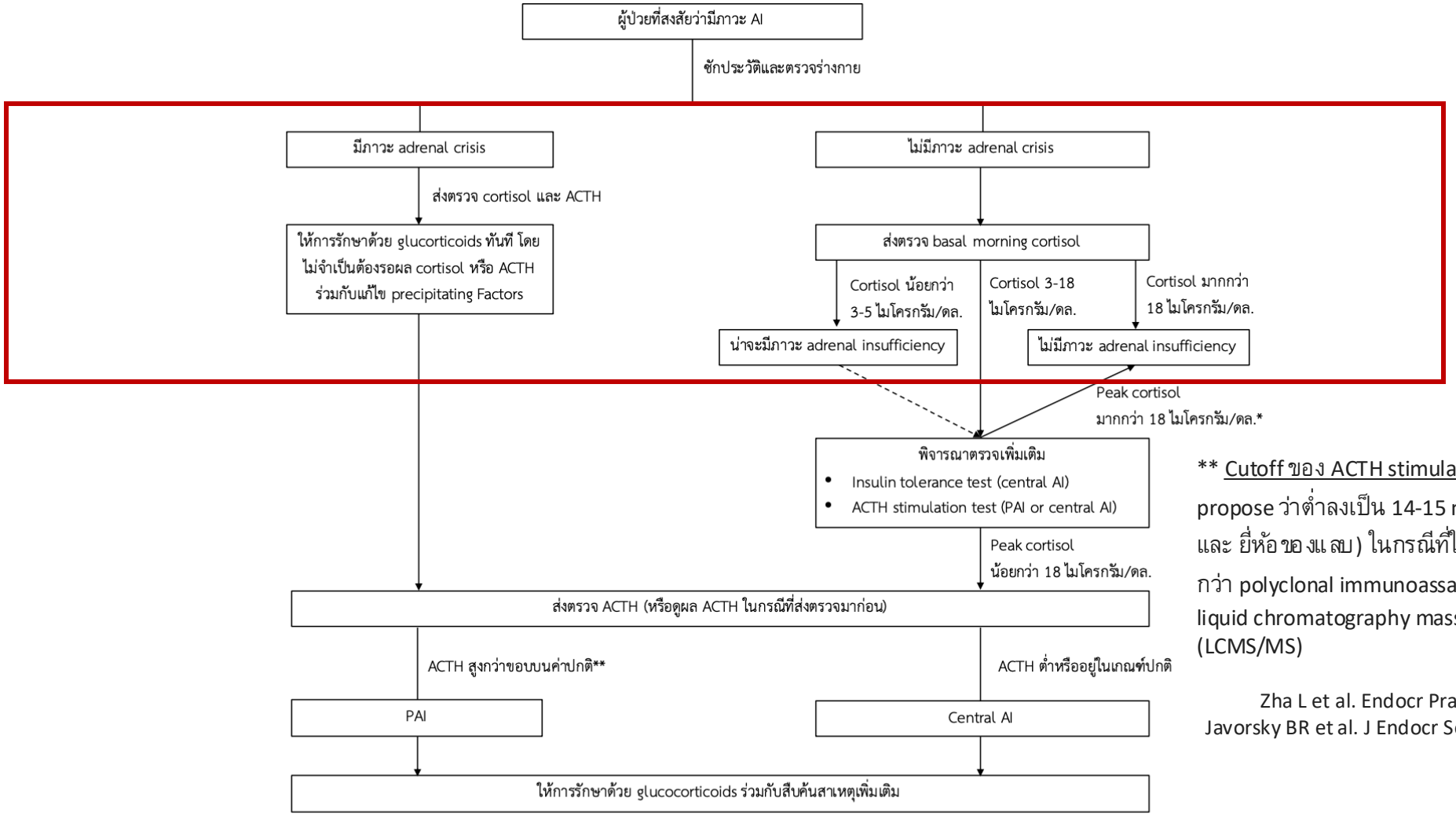


Image from Williams textbook of endocrinology 13th edition

Approach to Patients with Suspected Adrenal Insufficiency



AI, adrenal insufficiency; ACTH, adrenocorticotrophic hormone; PAI, primary adrenal insufficiency

*หมายเหตุ ในกรณีที่ยังสงสัยว่าผู้ป่วยอาจมีภาวะ AI พิจารณาติดตามใกล้ชิด

**หมายเหตุ ACTH มักมีค่าสูงกว่า2 เท่าของขอบบนค่าปกติ (upper limit ของ reference range)

** Cutoff ของ ACTH stimulation test ในปัจจุบัน มี propose ว่าต่ำลงเป็น 14-15 mcg/dL (ขึ้นอยู่กับ assay และ ยี่ห้อของแลบ) ในกรณีที่ใช้ assay อื่นๆ ที่ specific กว่า polyclonal immunoassay เช่น monoclonal หรือ liquid chromatography mass spectrometry (LCMS/MS)

Zha L et al. Endocr Pract 2022. PMID: 35487459.
Javorsky BR et al. J Endocr Soc 2021. PMID: 33768189.

Adrenal Crisis

- ***Adrenal crisis = medical emergency***
- Patients may manifest with signs and symptoms of circulatory failure
- Most severe manifestation of adrenal insufficiency
  - Could result from either primary or central adrenal insufficiency
- Mortality rate ~ 6%
  - It may contribute to increased mortality attributed to infectious disease among patients with hypoadrenalism

Symptoms, signs & biochemical characteristics of adrenal crisis
Symptoms • Anorexia, nausea, vomiting • Severe fatigue • Postural dizziness, syncope • Confusion
Signs • Hypotension • Impaired consciousness • Fever
Biochemical abnormalities • Hyponatremia • Hypoglycemia • Eosinophilia

Rushworth RL, Torpy DJ, Falhammar H. Adrenal Crisis. N Engl J Med. 2019 Aug 29;381(9):852-861.

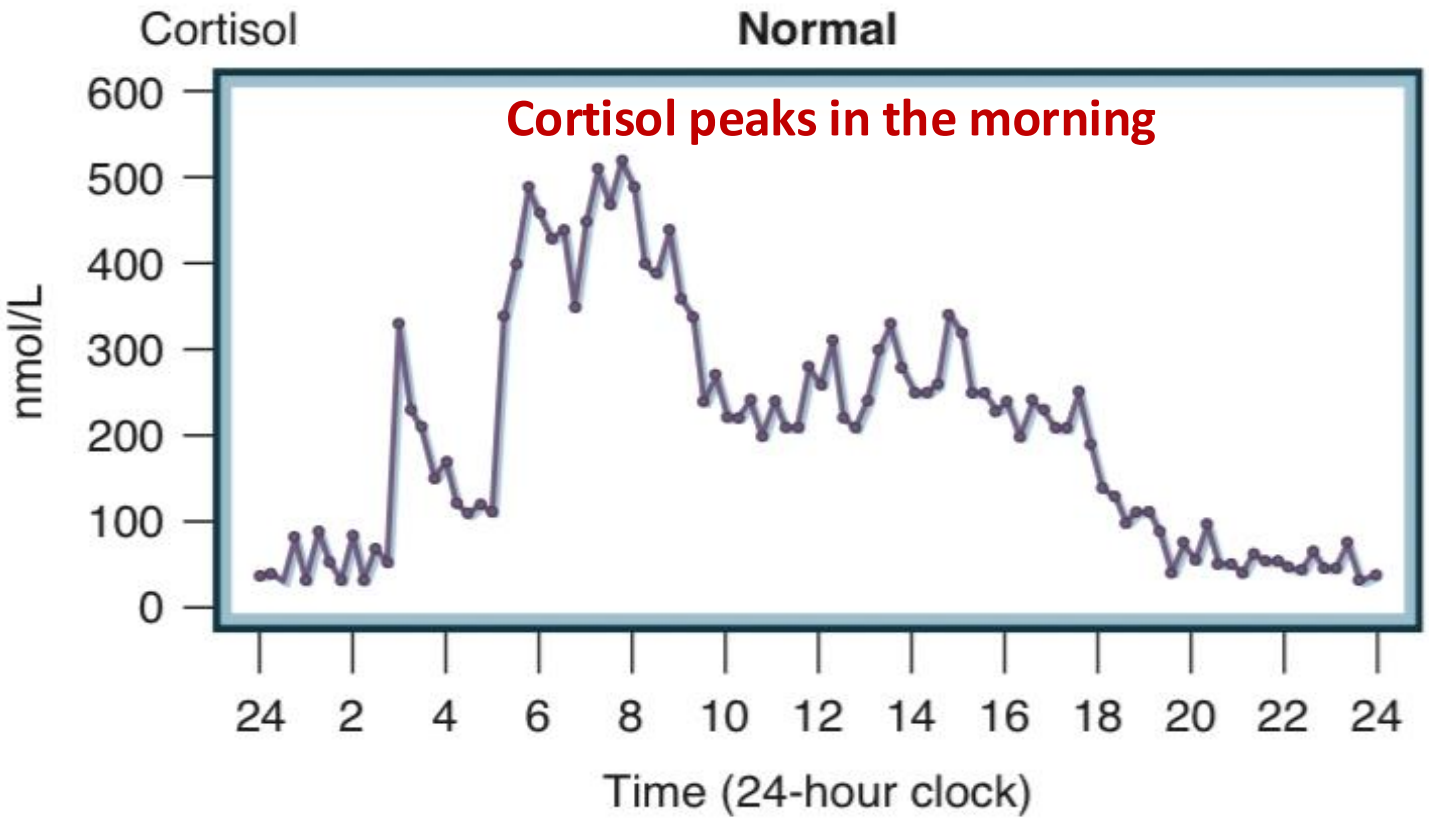
Adrenal Crisis

- If an adrenal crisis is suspected
  - **Draw blood for cortisol & ACTH** **** Do not wait for cortisol results to start treatment****
- Prompt treatment with glucocorticoids is needed
  - ***Hydrocortisone 100 mg IV (or IM) bolus, then 200 mg in 24 hrs***
    - Alternatives:
      - Dexamethasone 4 mg q 24 hrs
      - Prednisolone 25 mg then 25 mg x 2 doses (total 75 mg/24 hrs)
      - Methylprednisolone 40 mg q 24 hrs
  - Others: IV fluid, correct precipitating factors
- Symptoms will be markedly improved after 1-2 hours of parenteral glucocorticoid administration

Rushworth RL, Torpy DJ, Falhammar H. Adrenal Crisis. N Engl J Med. 2019 Aug 29;381(9):852-861.

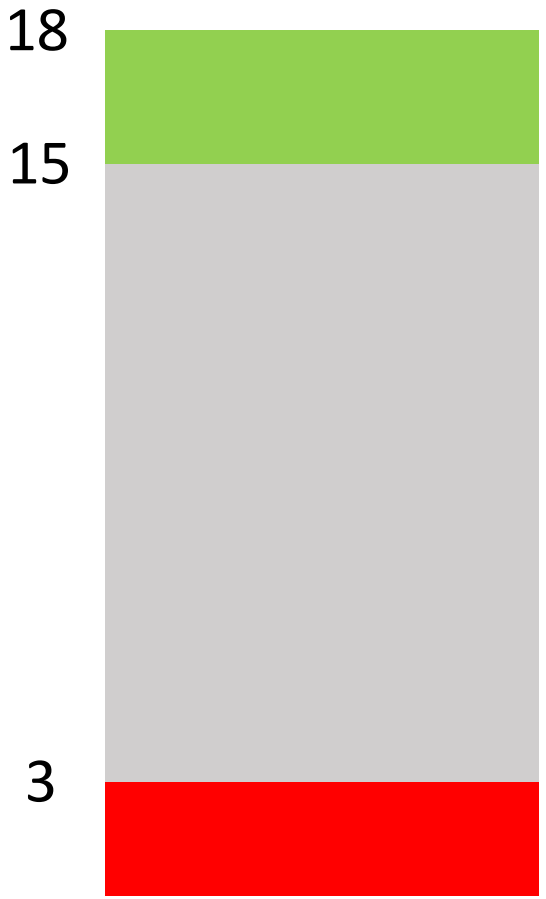
Diagnosis

- Initial test: Morning cortisol (7-9 am)



Williams textbook of endocrinology 14th edition

Morning cortisol



Cortisol > 15 μg/dL
→ Likely excludes adrenal insufficiency

Cortisol 3-15 μg/dL → Dynamic testing

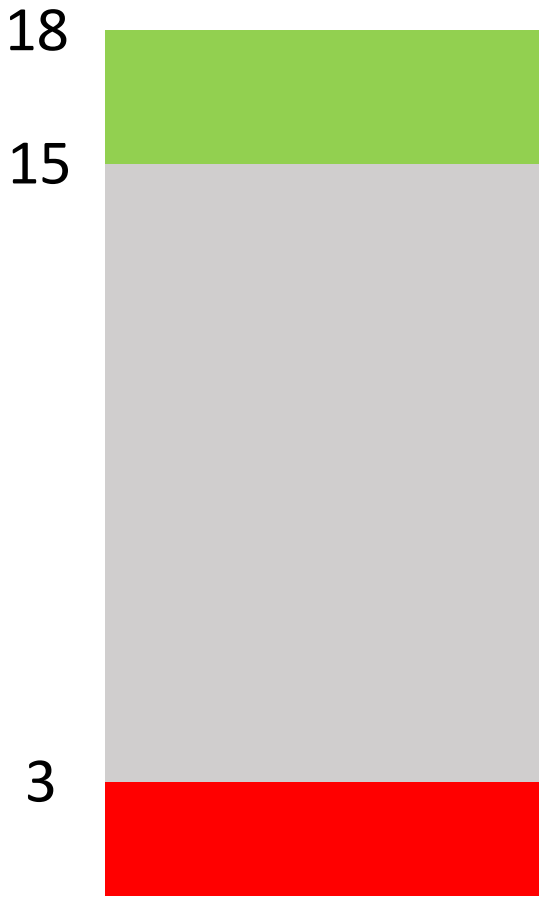
- Insulin tolerance test (ITT)
- ACTH stimulation test

Cortisol < 3-5 μg/dL
→ Indicative of adrenal insufficiency

Excellence Center
In Diabetes, Hormone and Metabolism
King Chulalongkorn Memorial Hospital

Bornstein SR, Allolio B, Arlt W et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 Feb;101(2):364-89.

Morning cortisol



Cortisol 3-15 μg/dL → Dynamic testing

Low cortisol in combination with elevated ACTH → "highly predictive for primary adrenal insufficiency"

- 8 AM cortisol < 5 mcg/dL & ACTH > 2-fold upper normal limit or reference ranges

Endocrine society guidelines for management of primary adrenal insufficiency 2016

Excellence Center
In Diabetes, Hormone and Metabolism
King Chulalongkorn Memorial Hospital

J Clin Endocrinol Metab 101: 0000–0000, 2016

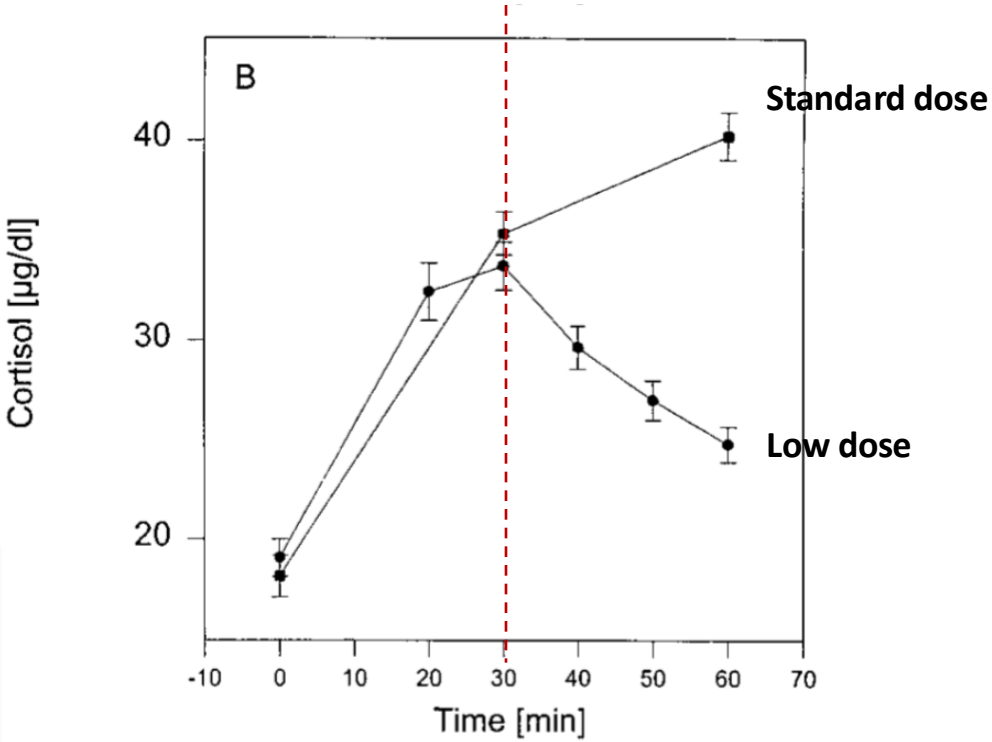
ACTH Stimulation Test

- Using synthetic ACTH-(1–24)
  - High dose or standard dose (250 mcg)
  - Low dose (1 mcg)
- Measure cortisol level at 30 or 60 min (or 20 & 40 min)
  - Peak cortisol < 18-20 mcg/dL → indicates adrenal insufficiency

Recent studies showed that the cutoff of peak cortisol lowered to 14-15 mcg/dL when using newer cortisol assays.

Zha L et al. Endocr Pract 2022. PMID: 35487459.
Javorsky BR et al. J Endocr Soc 2021. PMID: 33768189.

Mean cortisol level at 30 min in both groups were not significantly different (*P*=0.077).



Cortisol response following ACTH stimulation

Mayenknecht J et al. Comparison of low and high dose corticotropin stimulation tests in patients with pituitary disease. J Clin Endocrinol Metab. 1998 May;83(5):1558-62.
Abdu TA et al. Comparison of the low dose short synacthen test (1 microg), the conventional dose short synacthen test (250 microg), and the insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in patients with pituitary disease. J Clin Endocrinol Metab. 1999 Mar;84(3):838-43.
Ospina NS et al. ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2016 Feb;101(2):427-34.

Insulin Tolerance Test

- Gold standard in the diagnosis of central adrenal insufficiency
- Administer insulin, 0.05-0.15 U/kg iv
- Sample blood at -30, 0, 30, 60 & 120 min for;
  - cortisol, glucose
- Glucose < 40 mg/dL → peak cortisol > 18.1 -20 μg/dL

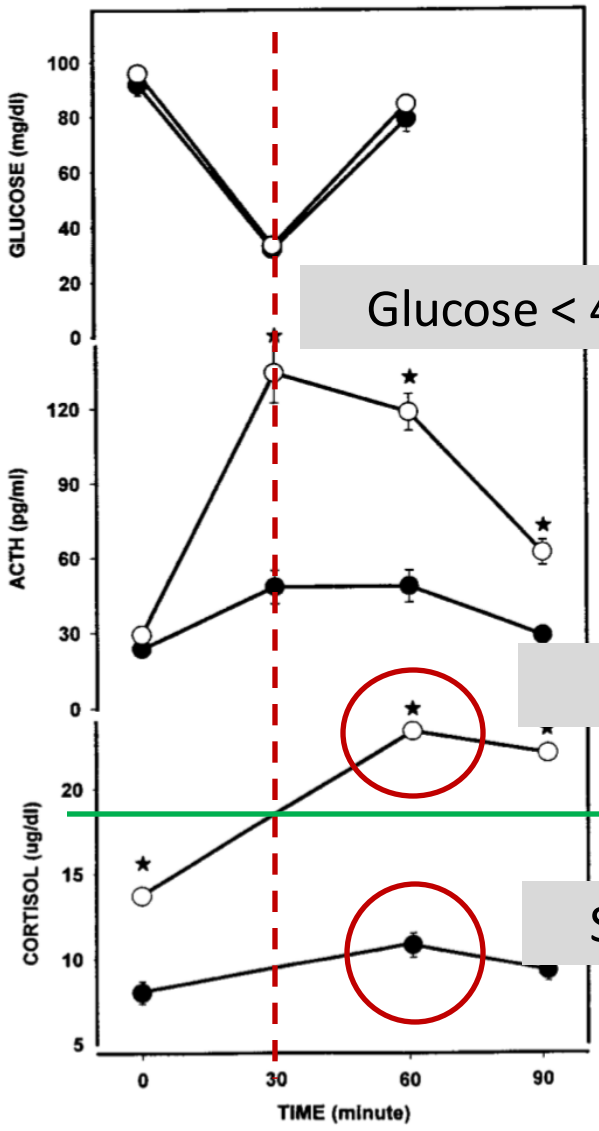
J Clin Endocrinol Metab 101: 0000–0000, 2016

Insulin Tolerance Test

- Contraindication
  - Ischemic heart disease/arrhythmia
  - Epilepsy
- Not advisable in children and the elderly

Fleseriu M et al. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016.

Insulin Tolerance Test



Glucose < 40 mg/dL

Normal response

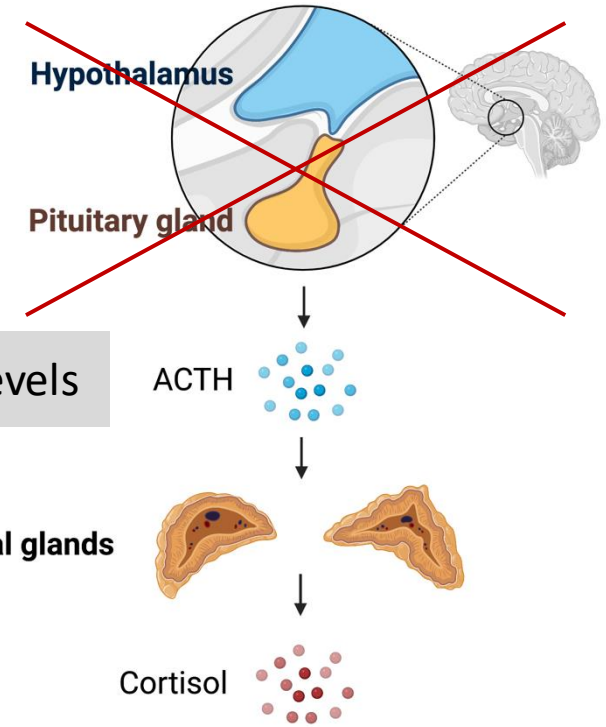
Cortisol >18.1-20.0 μg/dL

Subnormal response

Erturk E, Jaffe CA, Barkan AL. Evaluation of the integrity of the hypothalamic-pituitary-adrenal axis by insulin hypoglycemia test. J Clin Endocrinol Metab. 1998.

ACTH level: to differentiate between central and primary adrenal insufficiency

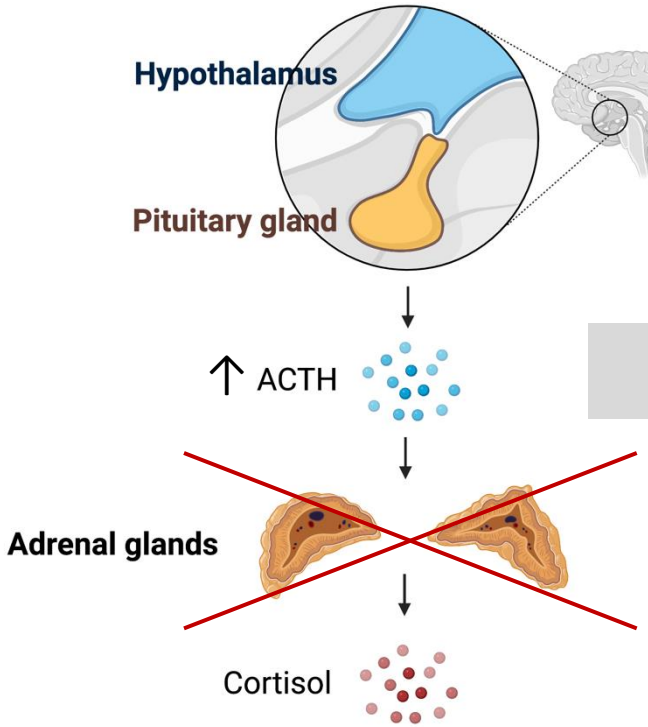
Central adrenal insufficiency



Normal or low ACTH levels

MRI pituitary

Primary adrenal insufficiency



High ACTH levels

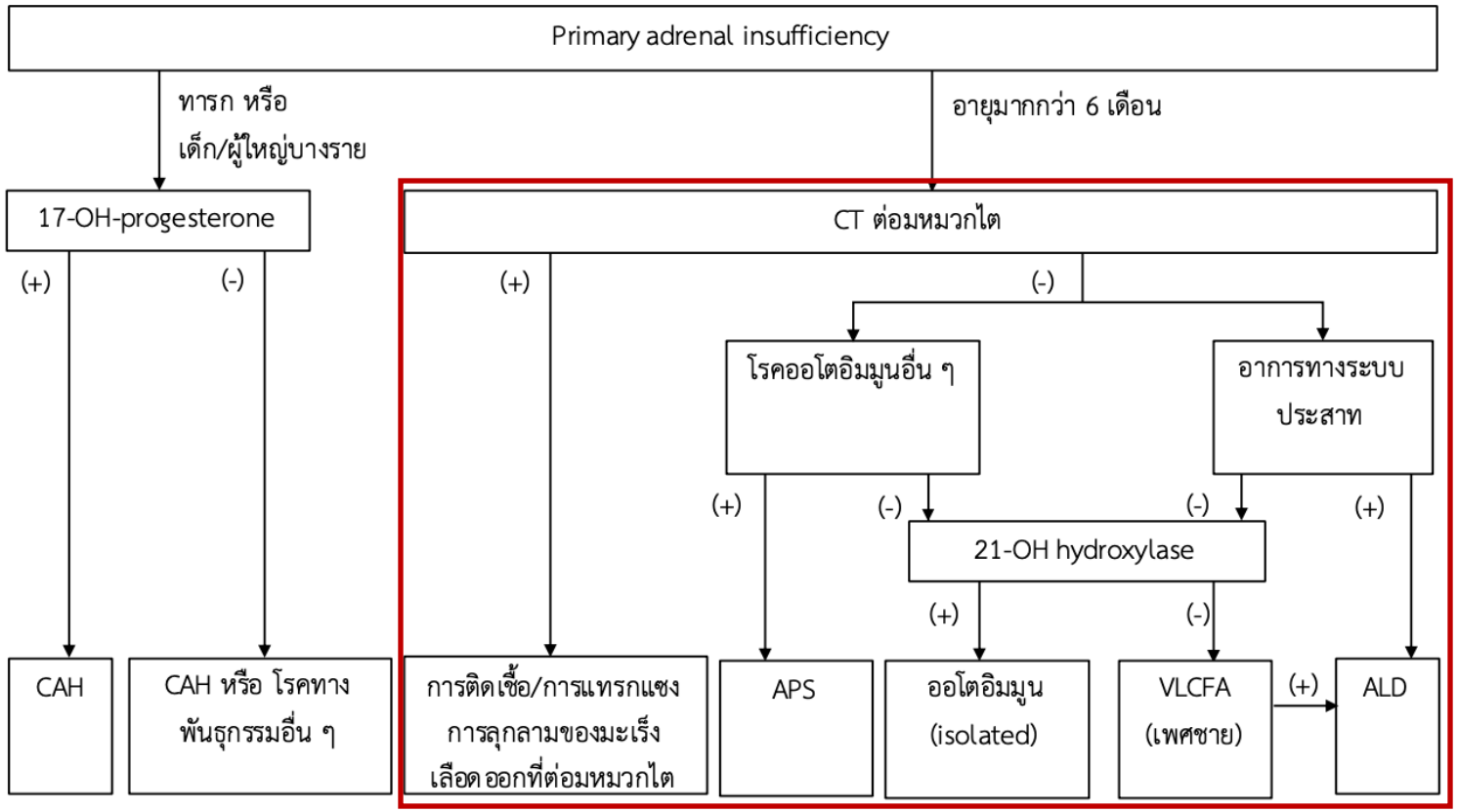
CT adrenal glands

ACTH: Specimen Handling Technique

- Collected in pre-chilled EDTA tube
- Transported on ice to the lab
- ACTH is rapidly degraded → falsely low results
  - If not processing right away, it must be centrifuged immediately and kept at -20 °C

Clin Biochem. 36(2):109-12, 2003.

Approach to Patients with Primary Adrenal Insufficiency



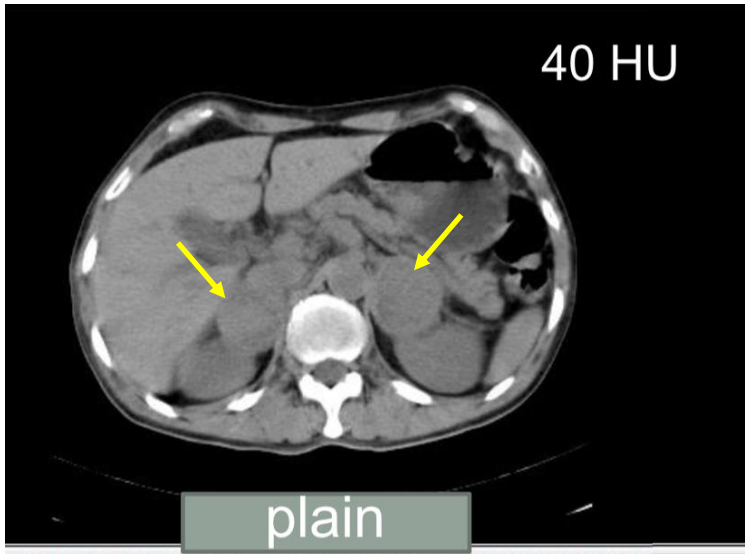
CT, computed tomography; CAH, congenital adrenal hyperplasia; APS, autoimmune polyendocrine syndrome; VLCFA, very long chain fatty acid; ALD, adrenoleukodystrophy

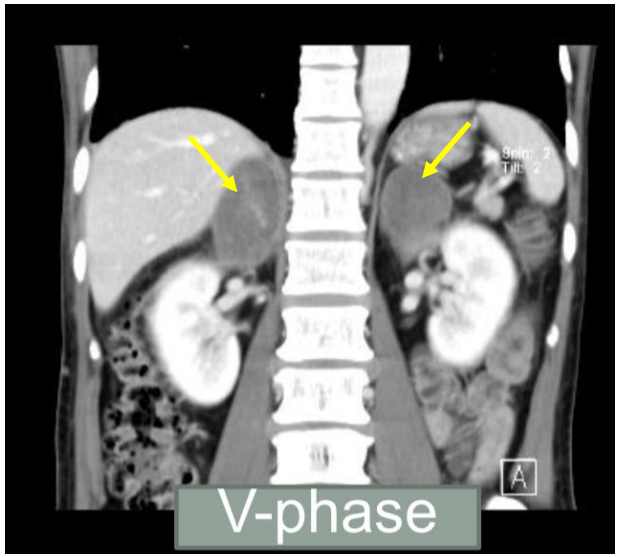
หมายเหตุ ในกรณีที่ 17-OH-progesterone สูงมากกว่า 10,000 นาโนกรัม/ดล. สามารถให้การวินิจฉัย CAH ได้

วาสิตา วราชิต ภาคสุข. “Adrenal insufficiency” Inpatient medical consultation การรับปรึกษาผู้ป่วยในทางอายุรศาสตร์. พิมพ์ครั้งที่ 1. กรุงเทพมหานคร

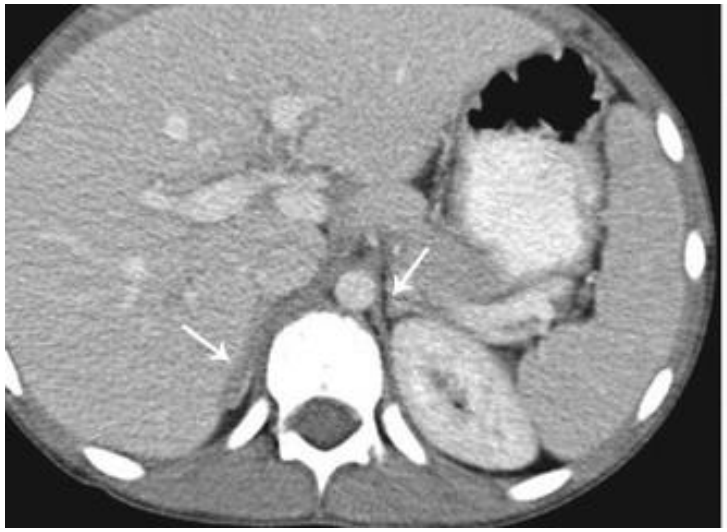
CT Adrenal Glands

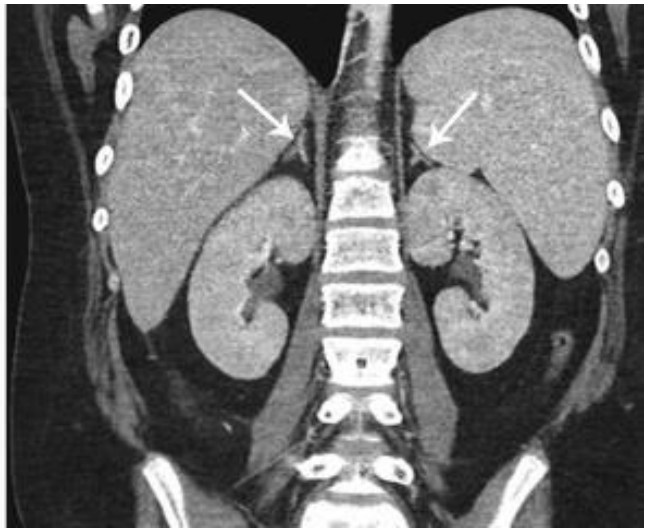
Adrenal histoplasmosis





Normal adrenal glands on CT





Images from https://radiologykey.com/adrenal-gland-imaging/

Adrenal Insufficiency: Treatment

👉 การรักษา

- Glucocorticoids:
  - หลักการ = ใกล้เคียง physiologic dose มากที่สุด (ถ้าขนาดมากไป → iatrogenic Cushing's syndrome แต่ถ้าน้อยไป → adrenal crisis)
    - Hydrocortisone 15-25 mg/day (2-3 ครั้ง/วัน) หรือ Prednisolone 3-5 mg/day (1-2 ครั้ง/วัน)
      - Dose ละเอียดๆ คือ 5-8 mg/m^2
    - หลีกเลี่ยง dexamethasone ในการ replacement เนื่องจากมี Cushingoid side effects เยอะ
  - Surgery/illness → ปรับเพิ่มขนาดตาม stress
  - กรณีที่ผู้ป่วยกินไม่ได้ → เปลี่ยน route เช่น SC, IM
  - Pregnancy → prefer hydrocortisone > prednisolone > dexamethasone (ผ่านรก)
- Central AI:
  - Other pituitary hormonal replacement, e.g., LT4 ในคนที่มี central hypothyroidism, etc.
- Primary AI:
  - Mineralocorticoids: fludrocortisone 50-100 mcg/day ในคนที่มี deficiency
  - Sex steroid: สามารถให้ DHEA ในผู้หญิง low libido, low energy level แม้จะได้การรักษาสองอย่างข้างต้นดีแล้ว

👉 Monitor: BW, อาการทั่วไป (BP, postural hypotension), electrolyte, well-being

👉 Patient education: steroid emergency card, sick day management → prevent adrenal crisis

👉 Genetic counseling ในโรคที่ถ่ายทอดทางพันธุกรรม

Reference:

1. Stewart PM, Newell-Price JDC. The adrenal cortex. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology. 13th ed. Philadelphia, PA: Elsevier; 2016:490-555.
2. Bornstein SR, Aliolio B, Arit W, et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 101: 364–389, 2016

Steroid Management in Specific Situation

Condition	Suggested Action
Home management of illness + fever	Hydrocortisone dose x 2 if BT >38˚C Hydrocortisone dose x 3 if BT >39˚C
Unable to tolerate oral medication	Hydrocortisone 100 mg im or sc
Minor-moderate surgical stress	Hydrocortisone 25-75 mg/24 h
Major surgery	- Hydrocortisone 100 mg iv then 200 mg iv drip in 24h or 50 mg q 6 h iv or im - Rapid tapering and switch to oral regimen

Other procedures, e.g. dental procedure (extra morning dose 1 h before surgery, double the oral dose for 24 h then return to normal dose after sugery)

1. Bornstein SR, Allolio B, Arlt W et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 Feb;101(2):364-89. 2. European Journal of Endocrinology (2015) 172, R115–R124 3. UK Addison's disease self-help group; www.addisons.org.uk.

Patient education & Identification

- Sick day management
- Discussing signs & symptoms of adrenal insufficiency
- Situation which required dose adjustment
- Steroid emergency card

Bornstein SR et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 Feb;101(2):364-89.

Take home message

- Adrenal insufficiency is common & deadly if untreated.

- If adrenal crisis is suspected;
  - blood samples are needed: cortisol and/or ACTH
  - Prompt treatment with glucocorticoids is needed without awaiting lab results.
- If no adrenal crisis
  - Initial investigation: morning cortisol (7-9 AM)
  - Dynamic testing may be required
  - ACTH – to differentiate between primary and central adrenal insufficiency

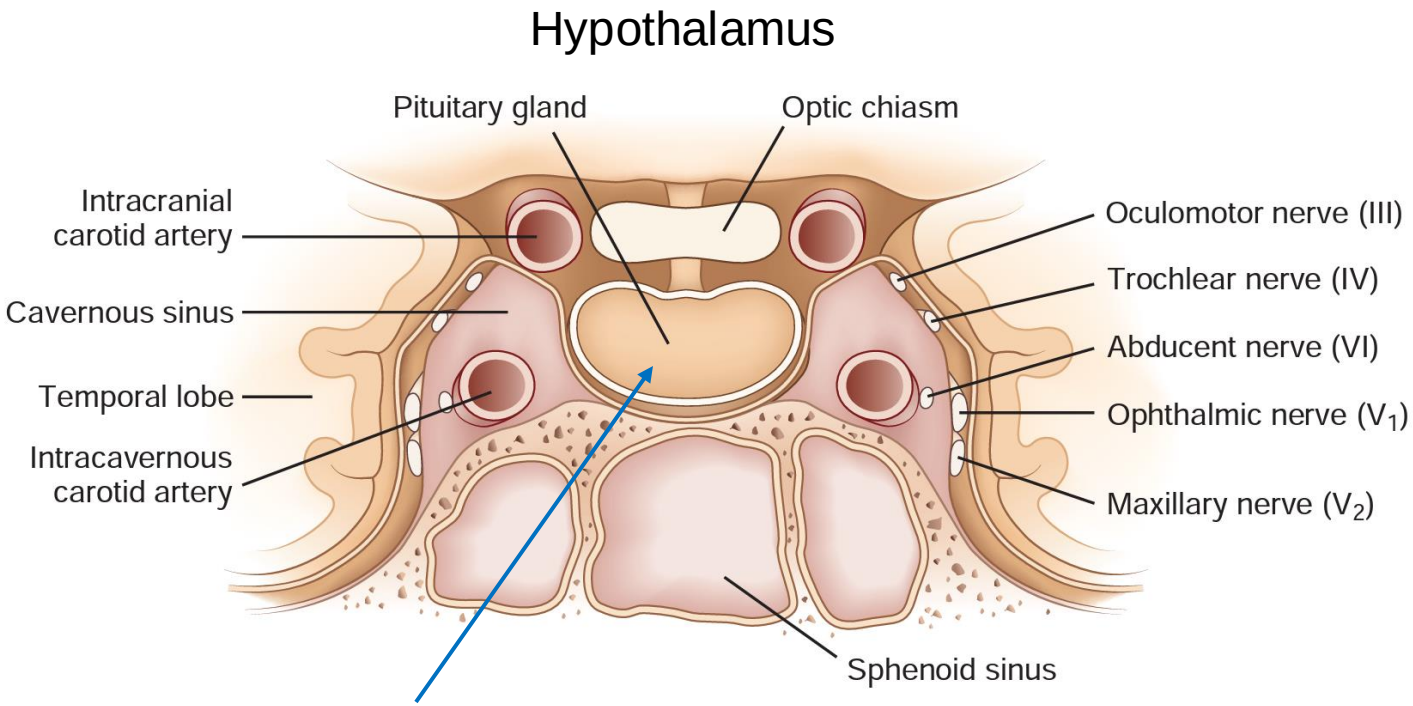
Hypopituitarism & Pituitary Tumors

Clinical Signs

- Local effect
- Pituitary hormones
  - Hypofunction
  - Hyperfunction

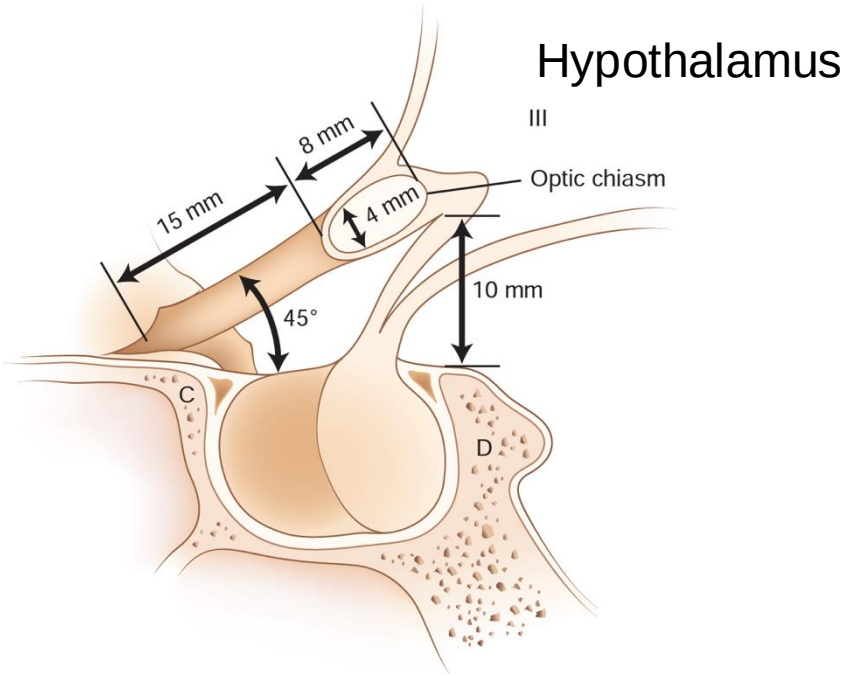
Clinical Signs: Local Effects

Coronal view



Sella turcica

Sagittal view



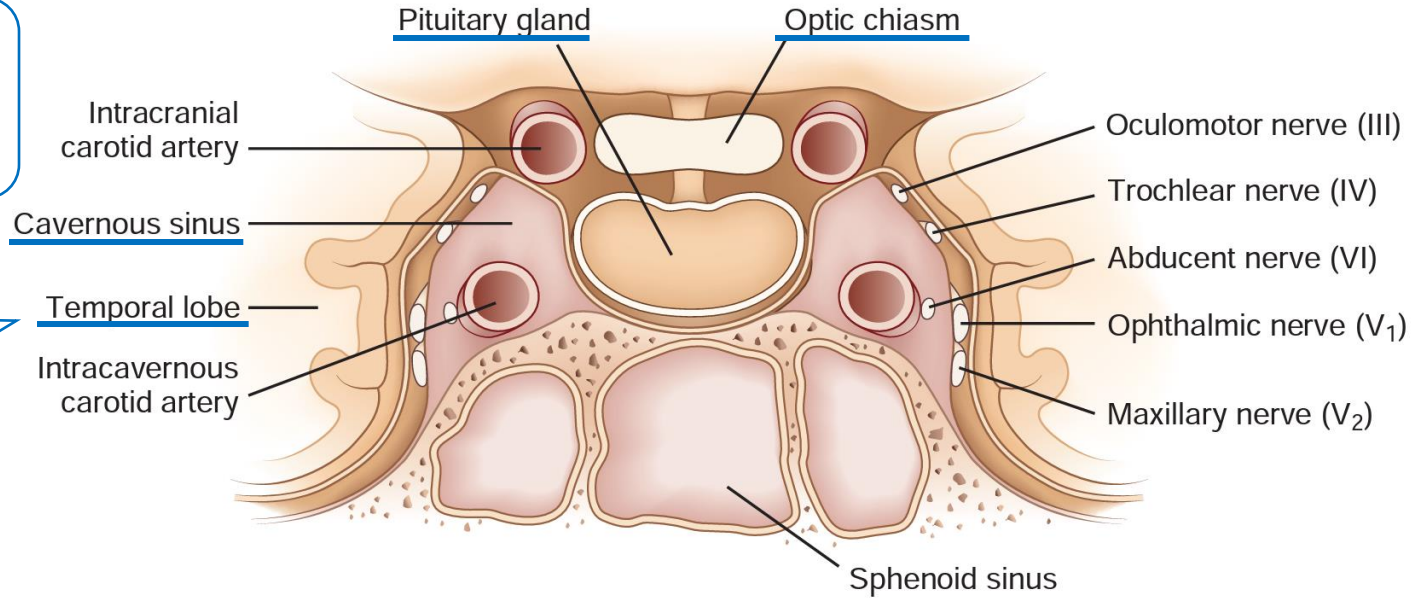
Williams Textbook of Endocrinology 13th edition.

Clinical Signs: Local Effects

- Loss of red perception
- Bitemporal hemianopia
- Superior/bitemporal field defect
- Blindness

Hypopituitarism

- Ptosis
- Diplopia
- Ophthalmoplegia



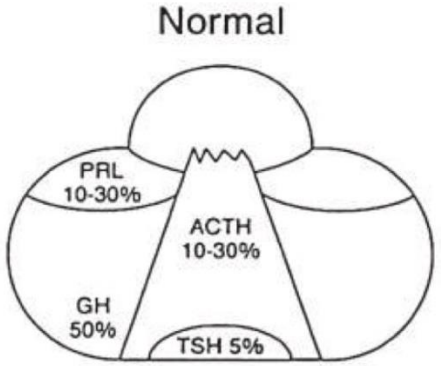
Uncinate seizures

Central: Headache, hydrocephalus, laughing seizures
Hypothalamus: Temperature dysregulation, obesity, diabetes insipidus (AVP deficiency)
Frontal lobe: Personality disorder

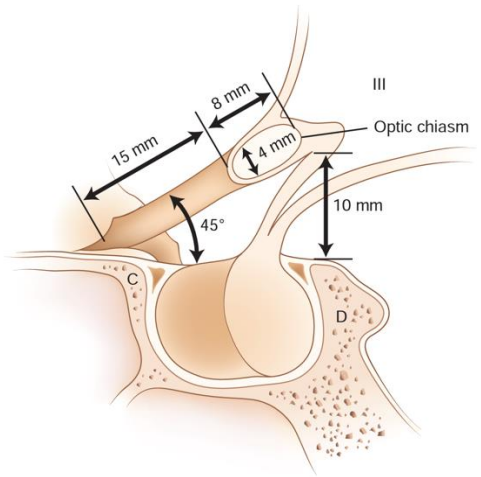
Williams Textbook of Endocrinology 14th edition

Hormonal Evaluation: Hypopituitarism

Anterior Pituitary



Posterior Pituitary



General

- Fatigue, weakness, decreased exercise capacity (TSH, ACTH, FSH/LH, GH)
- ↑ /↓ Weight (TSH, ACTH)

Gastrointestinal

- Anorexia, Nausea/vomiting (ACTH)
- Constipation (TSH)

Vasopressin

- Polyuria
- Persistent thirst throughout day & night
- Desire for cold liquids

Cardiovascular/metabolic

- ↓lean body mass, ↑fat mass (GH)
- Hypertension, bradycardia, impaired cardiac function (TSH)
- Dyslipidemia, Impaired glucose tolerance (TSH, GH)

Reproductive

- Oligo/amenorrhea (TSH, ACTH, FSH/LH)
- ED, low libido, vaginal dryness (FSH/LH)

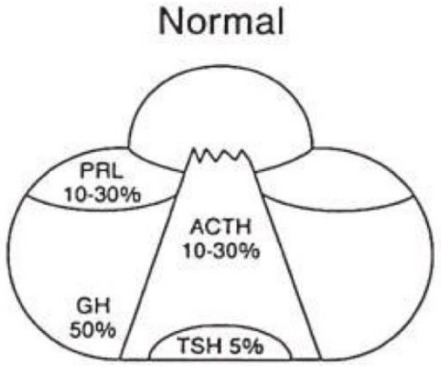
Skin

- Loss of body hair (TSH, ACTH, FSH/LH)
- Dry skin (TSH, ACTH)

J Clin Endocrinol Metab 101: 0000–0000, 2016

Hormonal Evaluation: Hypopituitarism

Anterior Pituitary



Disorder	Hormonal Measurement	Dynamic test
ACTH	8-9 AM cortisol	Insulin tolerance test ACTH stimulation test
TSH	FT4, TSH	Not recommended
GH	Single GH measurement = not recommended Except in patients with 3 other pituitary hormone deficiency	Insulin tolerance test GHRH + Arginine test Glucagon stimulation test
FSH/LH	FSH, LH, PRL T in male, E2 in female	Not recommended

GHRH, growth hormone releasing hormone; T, testosterone; E2, estradiol

J Clin Endocrinol Metab 101: 0000–0000, 2016

Diagnosis	N (N=2598)
Anterior pituitary mass	981
Cysts	79
Nonadenomatous neoplasms	46
Inflammatory and vasculitis	9
Infectious	2
Metastases	11
Vascular	22
Miscellaneous	43
Hypothalamic	4
Undiagnosed	159
Normal pituitary	1242

Anterior pituitary mass
- Prolactinoma (40%)
- Non-functioning adenoma (37%)
- Pituitary carcinoma (0.02%)

Cysts
- Rathke cleft cyst (53%)
- Craniopharyngioma (42%)

Nonadenomatous neoplasms
- Meningioma (70%)
- Chordoma (7%)

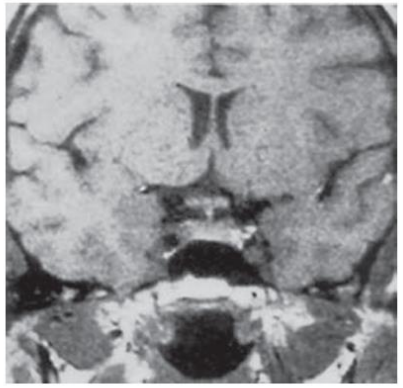
Metastases
- Breast cancer (30%)
- Others: lung, lymphoma, liver, nasopharyngeal carcinoma

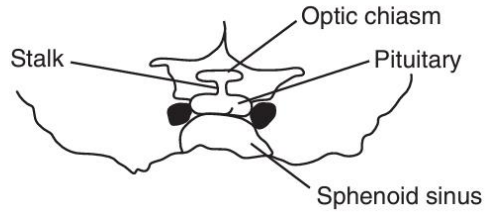
Miscellaneous
- Empty sella (49%)

J Clin Endocrinol Metab 96: 1633–1641, 2011

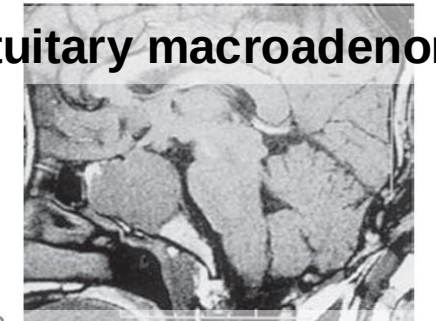
Pituitary Imaging: Look for Hypothalamic, Sellar/Parasellar Lesions!

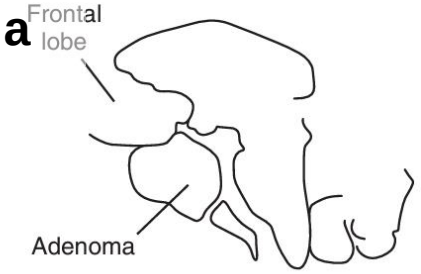
Normal MRI



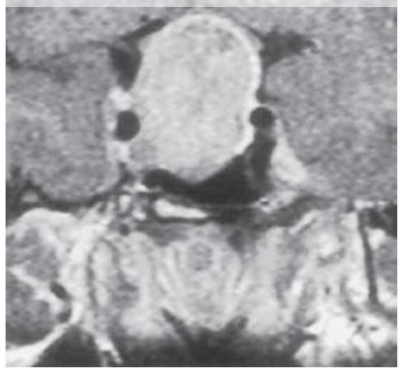


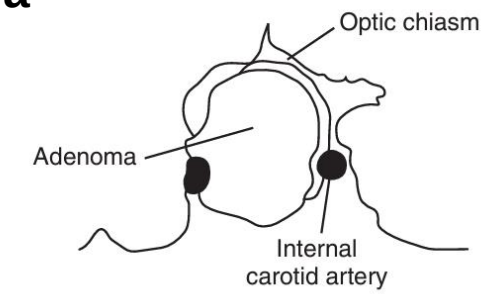
Pituitary macroadenoma

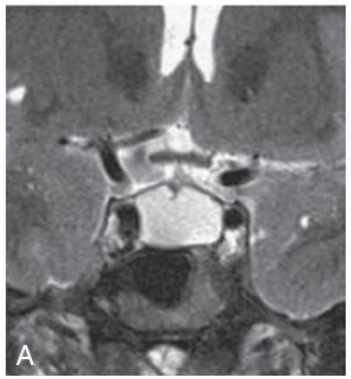


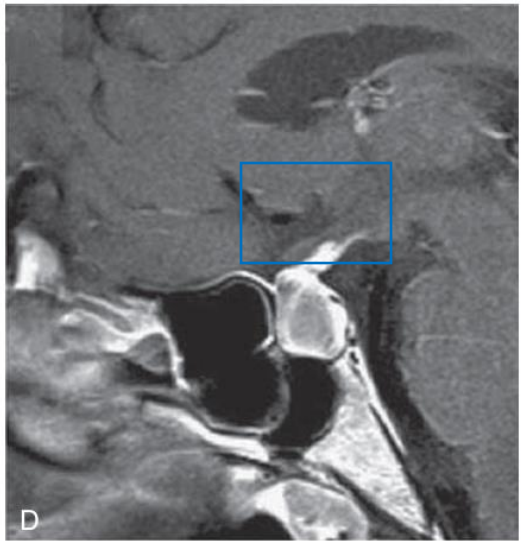


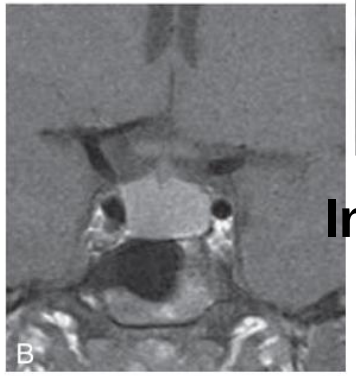
Pituitary macroadenoma











Infundibulohypophysitis

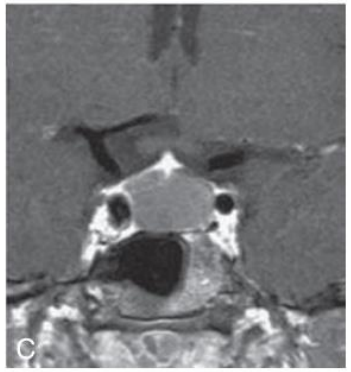
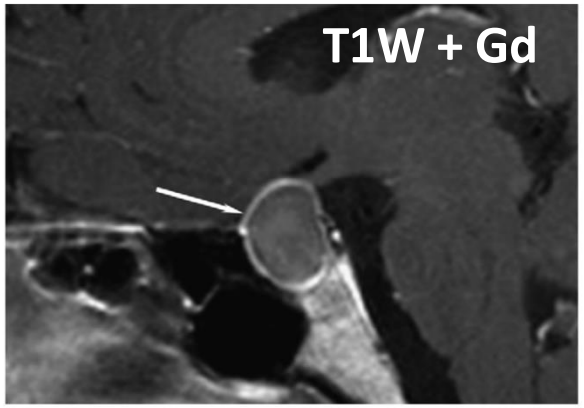


Image from Williams textbook of endocrinology 14th edition

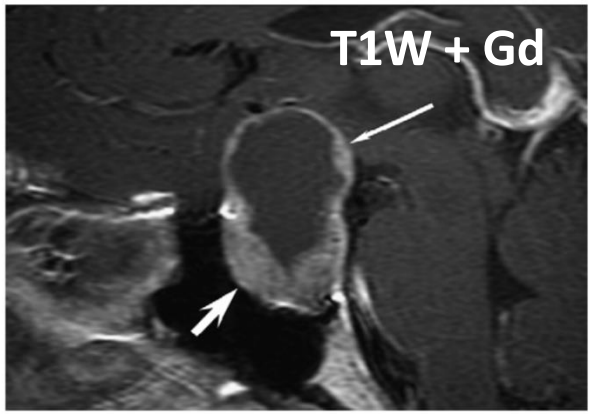
Pituitary Imaging

Rathke cleft cysts



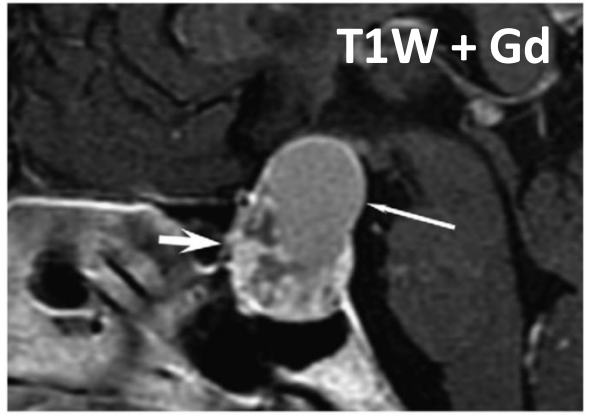
- An ovoid shape
- Small tumor volume
- Little or no cyst wall enhancement
- Rarely found calcifications

Pituitary adenomas with cystic degeneration



- A “snowman” shape
- Solid characteristics and homogeneous enhancement of the solid portion

Craniopharyngiomas

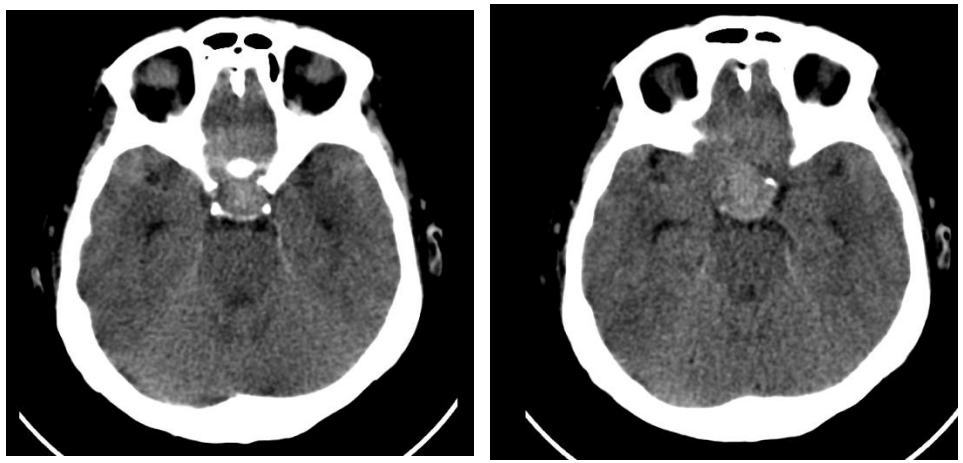


- Mixed solid and cystic characteristics
- Calcifications occurred in up to 80% (some types)
- Reticular enhancement of solid portions
- May have lobulated shape with third ventricle compression

Clinical Radiology (2007) 62, 453e462

A 66-year-old female presented with sudden severe headache

CT brain at 8 days after the onset of headache



Physical examinations

- BP 140/80 mmHg, PR 70 bpm
- E4M6V5
- Pupils 3 mm RTLBE (EOM/ptosis were not documented)

Laboratory investigations

- *Na 134 K 3.5 Cl 100 HCO_3 27*
- Hb 13.7 g/dl Hct 40 % WBC 5,800 (N 50% L 40%) Platelet 215,000
- PT 11.4 sec, INR 0.96, PTT 33.7 sec
- *FT4 0.28 ng/dl (0.54-1.24), TSH 1.74 uIU/ml (0.34-5.6)*
- 8 AM cortisol = 6 μg/dL

T1W

T2W

MRI pituitary (8 days after the onset of headache)

T1W + Gd

T1W + Gd

🌟6. Pituitary
🔥HOT🔥สอนอ่าน MRI ep 1
https://www.facebook.com/CUEZendocrine/posts/614892555371391
.
สอนอ่าน MRI ep2
https://www.facebook.com/CUEZendocrine/posts/618680144992632
.
MRI pituitary quiz
https://www.facebook.com/CUEZendo.../posts/619952024865444:0
.
pituitary apoplexy management
https://www.facebook.com/CUEZendocrine/posts/649527375241242
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Pituitary Apoplexy

- **A clinical syndrome**, characterized by;
  - *Sudden onset of headache, visual impairment and decreased consciousness caused by hemorrhage and/or infarction of the pituitary gland*

- It is a rare event
  - Prevalence: 6.2 cases per 100,000
  - Incidence: 0.17 episodes per 100,000 per year
- Occurred in male > female, age 5^{th} or 6^{th} decade

Endocrine Reviews 36: 622– 645, 2015

Pituitary Apoplexy

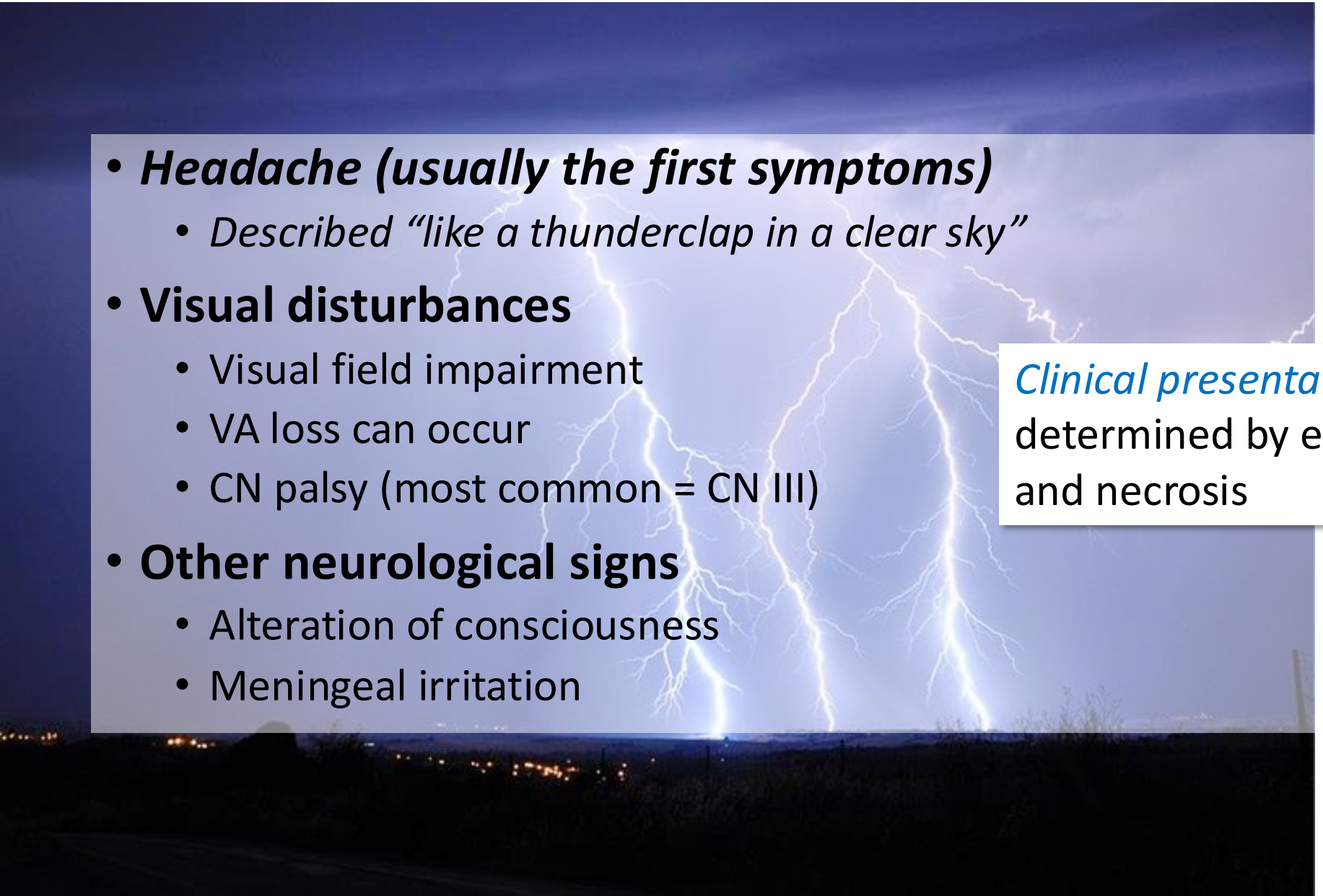
- 2-12% of patients with adenomas experienced apoplexy
  - More frequently observed in non-functioning pituitary adenomas
    - Generally discovered late and are usually larger than functioning adenomas
  - Other tumor types: prolactinomas, GH-secreting adenomas

- At the time of apoplexy
  - The diagnosis of pituitary tumor was unknown in 75% of patients
  - Precipitating factors were identified in 10-40% of patients.

Precipitating factors in pituitary apoplexy
• Major surgery, especially CABG
• Dynamic pituitary function tests
• Anticoagulation therapy
• Coagulopathies

Endocrine Reviews 36: 622– 645, 2015

Clinical Presentation



- ***Headache (usually the first symptoms)***
  - *Described "like a thunderclap in a clear sky"*
- **Visual disturbances**
  - Visual field impairment
  - VA loss can occur
  - CN palsy (most common = CN III)
- **Other neurological signs**
  - Alteration of consciousness
  - Meningeal irritation

Clinical presentation is highly variable, determined by extent of hemorrhage and necrosis

Endocrine Reviews 36: 622– 645, 2015

Endocrine Dysfunction

- ***Multiple acute endocrine insufficiencies*** can occur due to;
  - The destruction of the anterior pituitary
  - Increased intrasellar pressure on the pituitary stalk
- ***ACTH deficiency was reported in 50-80% of patients with apoplexy.***
  - Empirical steroids should be given to patients with pituitary apoplexy, without waiting for cortisol result.
- TSH deficiency and gonadotropin deficiency were reported in 40-75%.
- Diabetes insipidus is rare at onset.

Endocrine Reviews 36: 622– 645, 2015

Imaging

- ***MRI is the imaging procedure of choice***
  - Increased DWI signal in ischemic tissue is observed within a few minutes after arterial occlusion
- CT is usually the initial emergency examination for patients with severe headache of sudden onset.
  - It rules out subarachnoid hemorrhage
  - It shows an intrasellar mass in 80% of cases, with hemorrhagic components in 20%–30% of cases
  - After a few days, blood density decreases and may be more difficult to detect

Endocrine Reviews 36: 622– 645, 2015

Management:

- *Hydrocortisone was given and referred to KCMH*

At KCMH

- Prolactin 1.6 ng/mL (3-25)
- FSH 4.3 IU/L (1.6-9.3)
- LH 0.9 IU/L (2.4-9.3)
- IGF1 72.9 ng/mL (32-214)
- FT4 0.46 ng/dL (0.8-1.8), TSH 1.157 uIU/mL (0.3-4.1)

Impression:

- Non-functioning pituitary macroadenoma with pituitary apoplexy
- Panhypopituitarism

Genes Associated With Familial Pituitary Tumor Syndromes

Syndrome	Gene (Locus)	Most Frequent Mutation(s)	Pituitary Features	Other Features
MEN1	*MEN1* (11q13)	c.249-252delGTCT, an exon 2 predicted frameshift, in 4.5%	Pituitary adenoma in 30–40% (PRL 60%, NFA 15%, GH 10%, ACTH 5%, TSH rare)	Primary hyperparathyroidism, pancreatic tumors, foregut carcinoid tumors, adrenocortical tumors (usually nonfunctional), rarely pheochromocytomas, skin lesions (facial angiomas, collagenomas, and lipomas)
MEN1-like (MEN4)	*CDKN1B* (12p13)	Only two reported cases	Pituitary adenoma[a]	Primary hyperparathyroidism and single cases reported of renal angiomyolipoma, neuroendocrine cervical carcinoma
Carney complex	*PRKAR1A* (17q23-24)	c.491-492delTG in exon 5	Pituitary hyperplasia in most patients Adenoma in ~10% (GH and PRL)	Atrial myxomas, lentigines, Schwann cell tumors, adrenal hyperplasia
Familial, isolated pituitary adenomas	*AIP*[b] (11q13.3)	Gln14X nonsense mutation[c]	Pituitary adenoma (majority GH, PRL, or mixed GH and PRL)	Young patients, often macroadenomas with gigantism

[a]Only two reported cases to date: one GH-secreting adenoma and one ACTH-secreting adenoma.

[b]*AIP* mutations reported in 15% of individuals with familial isolated pituitary adenoma and 50% of those with isolated familial somatotropinomas.

[c]This is the most commonly identified mutation but is likely to be overrepresented secondary to a Finnish founder effect.

ACTH, Adrenocorticotrophic hormone; *GH,* growth hormone; *MEN1,* multiple endocrine neoplasia type 1; *NFA,* nonfunctioning adenoma; *NR,* not reported; *PRL,* prolactin.

From Elston MS, McDonald KL, Clifton-Bligh RJ, et al. Familial pituitary tumor syndromes. *Nat Rev Endocrinol.* 2009;5:453–461.

Williams textbook of endocrinology 14th edition

Polyuria

- Definition
  - Urine volume >40-50 mL/kg/day **OR** >3 L/day

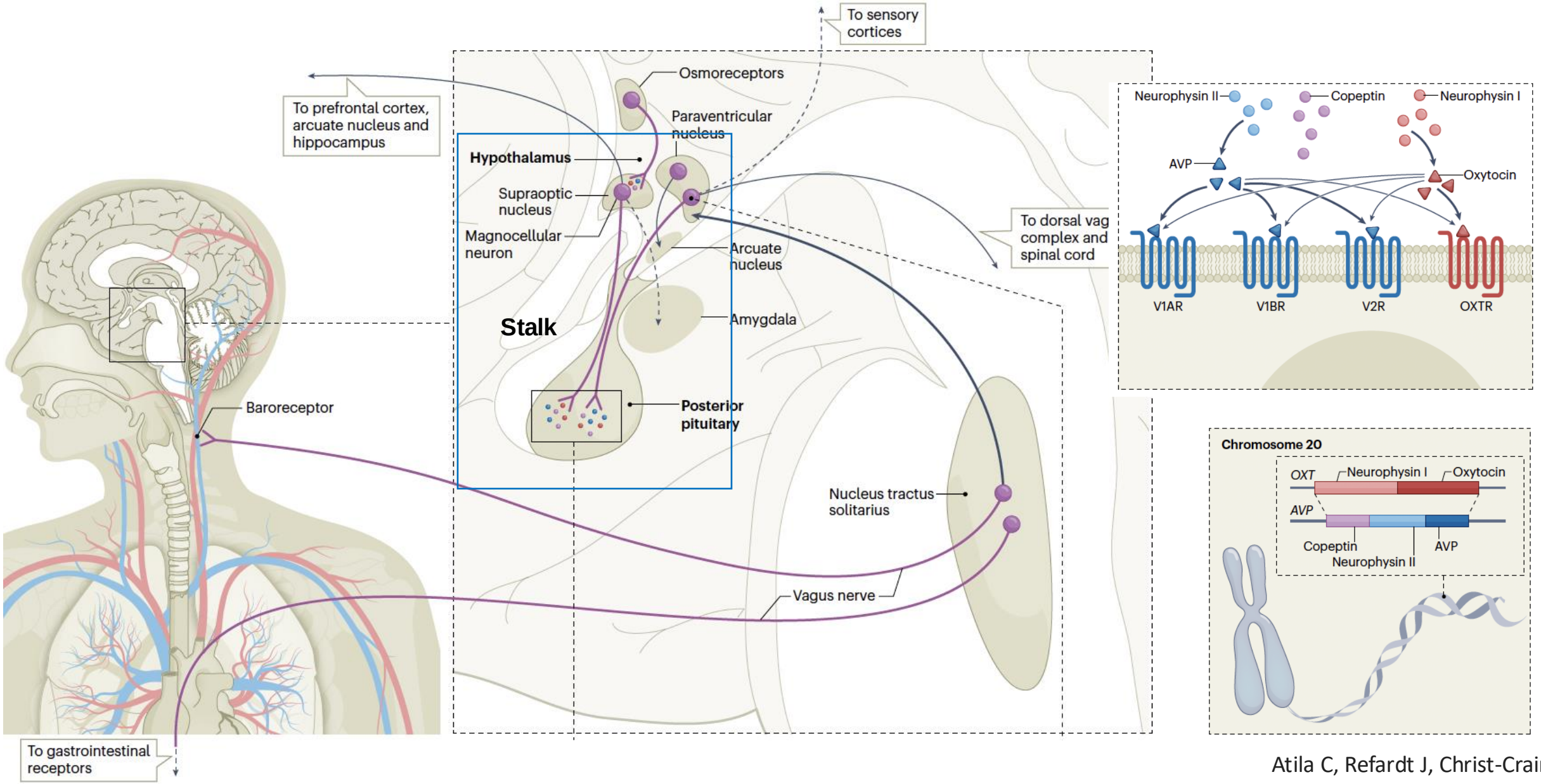
Polyuria ≠ Frequency

- Etiology
  - Water diuresis
    - AVP deficiency (known as “central DI”)
    - AVP resistance (known as “nephrogenic DI”)
    - Primary polydipsia
  - Solute diuresis
    - e.g., mannitol, hyperglycemia

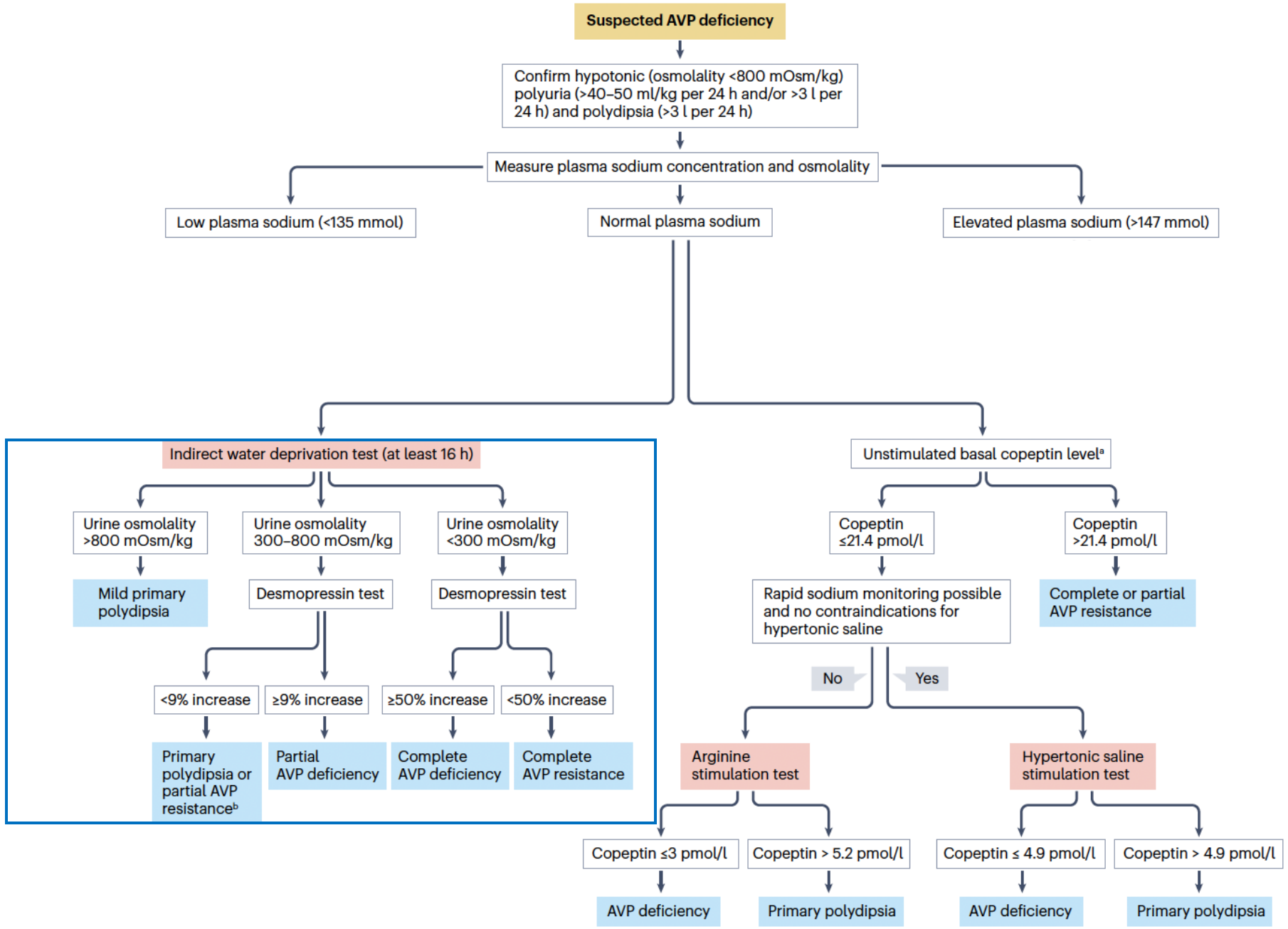
Diagnosis

- History
  - Onset, age, desire for cold liquids
  - Associated symptoms e.g., fever, weight loss, bone pain
- Physical examination
- Laboratory investigation
  - Electrolytes, serum/urine osmolarity
  - Additional test: water deprivation test
- Imaging
  - Posterior bright spot
  - Stalk/hypothalamic lesions

The Hypothalamic-Posterior Pituitary Axis



Atila C, Refardt J, Christ-Crain M.
Nat Rev Endocrinol 2024. PMID: 38693275.



Atila C, Refardt J, Christ-Crain M.
Nat Rev Endocrinol 2024. PMID: 38693275.

Water deprivation test

การเตรียมตัว

1. หลีกเลี่ยง alcohol อย่างน้อย 48 hrs, หลีกเลี่ยง nicotine และ caffeine อย่างน้อย 12 hrs ก่อนทำ test
2. ในกรณีที่ผู้ป่วยใช้ DDAVP อยู่แล้ว ให้หยุดยาก่อนมาทำ test อย่างน้อย 24 hrs
3. NPO โดยแพทย์กำหนดเวลา (พิจารณาตามปริมาณปัสสาวะ หากปริมาณปัสสาวะมาก ให้ NPO 6.00 น.)
4. ให้ผู้ป่วยชั่งน้ำหนักก่อนเริ่มทำ test

- Urine < 5 L/day -> NPO หลังเที่ยงคืน
- Urine > 10 L/day -> NPO หลัง 6.00
- Primary polydipsia -> NPO หลังอาหารเย็น

ขั้นตอนการทำ

1. ชั่งน้ำหนักตอนเริ่มอาการตรวจ (0 min)
2. เจาะ serum osmolarity และ ส่ง urine osmolarity ตอนเริ่มการตรวจ
3. เจาะ serum osmolarity (optional), ส่ง urine osmolarity และ ชั่งน้ำหนักตัวทุกชั่วโมง จนกระทั่ง (ข้อใดข้อหนึ่ง) ** ไม่ต้องครบทุกข้อ**
    a. น้ำหนักตัวลดลงจากเริ่มต้น 3-5%
    b. Urine osmolarity เปลี่ยนแปลงน้อยกว่า 10% *หรือ* 30 mOsm/kg ติดต่อกัน 2 ครั้ง (3 samples, ส่วนต่าง 2 ครั้ง)
    c. Serum osmolarity > 288 mOsm/kg
    d. Serum Na > 145 mmol/L
4. ฉีด DDAVP 1 mcg (0.25 mL) IV หรือ พ่น nasal solution 10 mcg (0.1 mL)
5. เจาะ serum osmolarity และ ส่ง urine osmolarity ต่อไปอีก 1-2 hrs หลังให้ DDAVP (optional)

Indirect Criteria of Miller-Moses Test

		Urine Osm	
		Before DDAVP	**After DDAVP**
AVP deficiency	Complete	< 300	> 50%
	Partial	300-800	9-50%
AVP resistance	Complete	< 300	< 9%
	Partial	< 300-500	9-50%
Polydipsia		> 500	< 9%

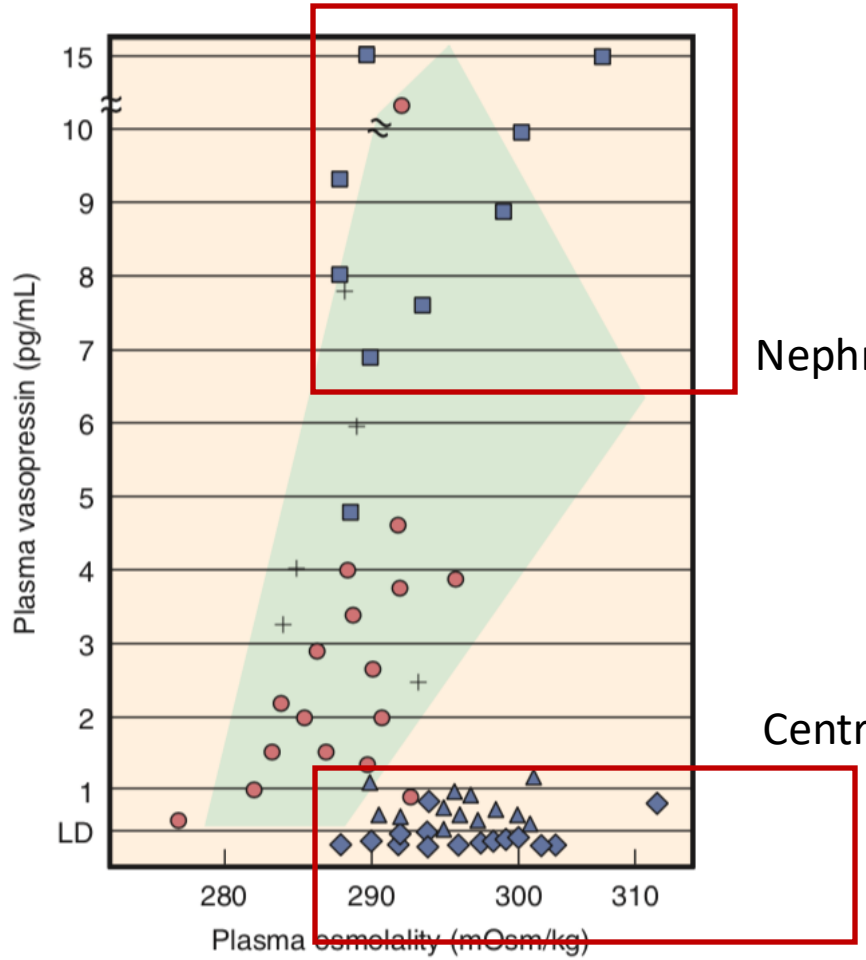


Figure 16.12 Relationship between plasma AVP and concurrent plasma osmolality in patients with polyuria of diverse causes. All measurements were made at the end of a standard dehydration test. *Shaded area,* Range of normal. In patients with severe (◆) or partial (▲) central DI, plasma AVP was almost always subnormal relative to plasma osmolality. In contrast, the values from patients with dipsogenic (●) or nephrogenic (■) DI were consistently within or above the normal range. (From Robertson GL: Diagnosis of diabetes insipidus. In Czernichow AP, Robinson A, editors: *Diabetes insipidus in man: frontiers of hormone research,* Basel, 1985, S Karger, pp 176.)

Relationship between pAVP & Concurrent Osmolarity

Interpretation of Water Deprivation

Time	Urine Osm.	Serum Osm.	BW (kg)
0	135	300	61.4
1 hr	141		61.2
2 hr	146	305	60.6
3 hr	270		60.6

DDAVP 0.1 mL NS

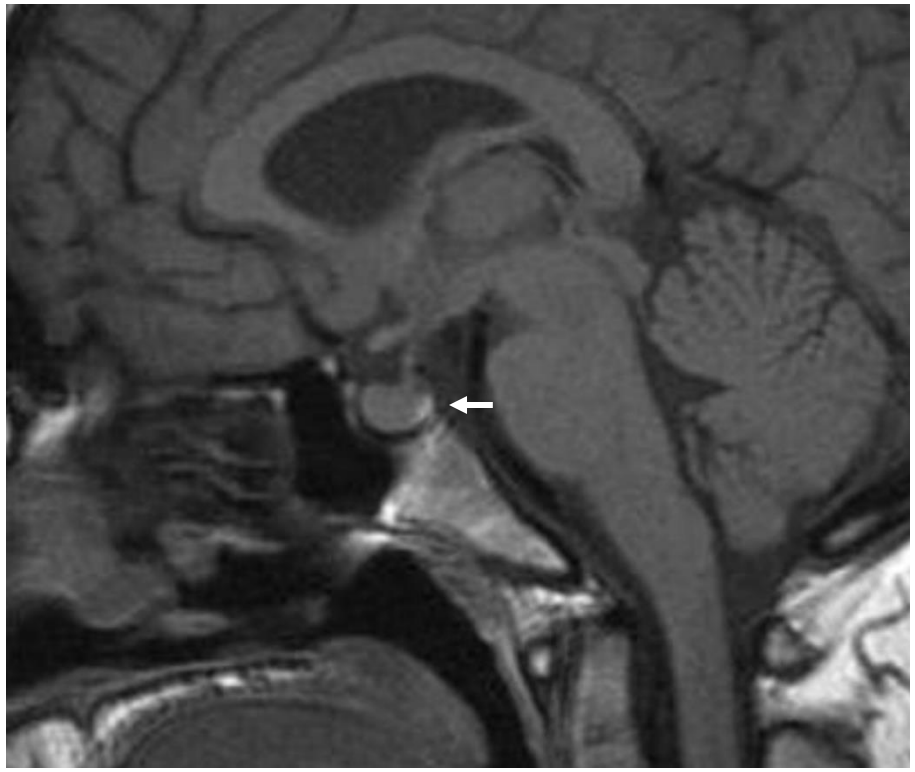
(270-146)/146 x 100 = 85%

Etiology of AVP Deficiency and AVP Resistance

	AVP Deficiency	AVP Resistance
Congenital	• AVP gene mutations (AD or AR) • Wolfram syndrome (AR) **DIDMOAD = DI, DM, optic atrophy, deafness**	• AVPR2 gene mutations (X-linked recessive) • AQP2 gene mutations (AR>AD)
Acquired	• Trauma • Tumors • Ischemic encephalopathy • Infiltrative • Autoimmune • Infectious diseases • Idiopathic	• Drug-induced • Hypercalcemia • Renal diseases • Infiltrating lesions of the kidney • Sickle cell disease or trait

Imaging

- Posterior bright spot
  - Appear bright in T1W
  - Present in ~80% of normal subjects.
  - Patients with AVP deficiency may have persistent bright spot
- Stalk lesions
- Hypothalamic lesions



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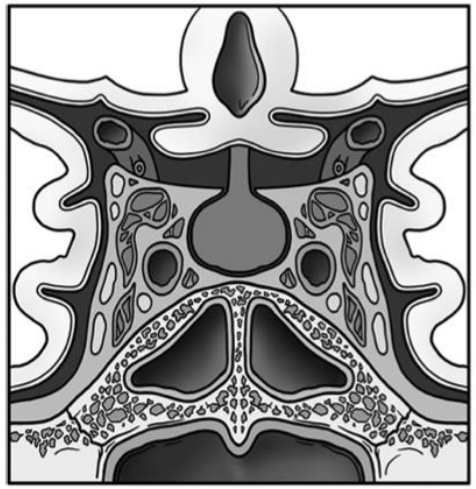
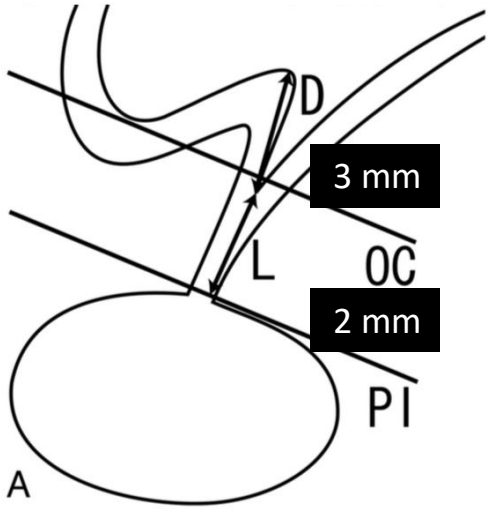
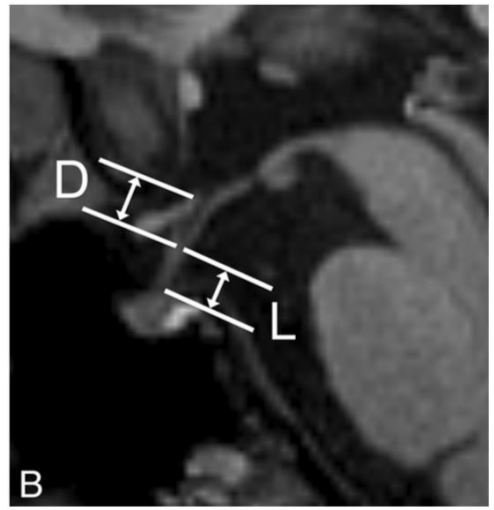
Stalk Measurement



Normal

AP





Lateral View

Consider stalk thickening

> 4 mm at optic chiasm

> 3 mm at pituitary insertion

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J Clin Endocrinol Metab 98: 1812–1818, 2013

Diseases Associated with Enlarged Stalk

- Germ cell tumor
- Craniopharyngioma
- Metastasis (e.g., CA breast, lung)
- Lymphocytic infundibulohypophysitis
- Langerhans & Non-Langerhans cell histiocytosis
- Granulomatosis with polyangiitis
- Sarcoidosis
- Tuberculosis

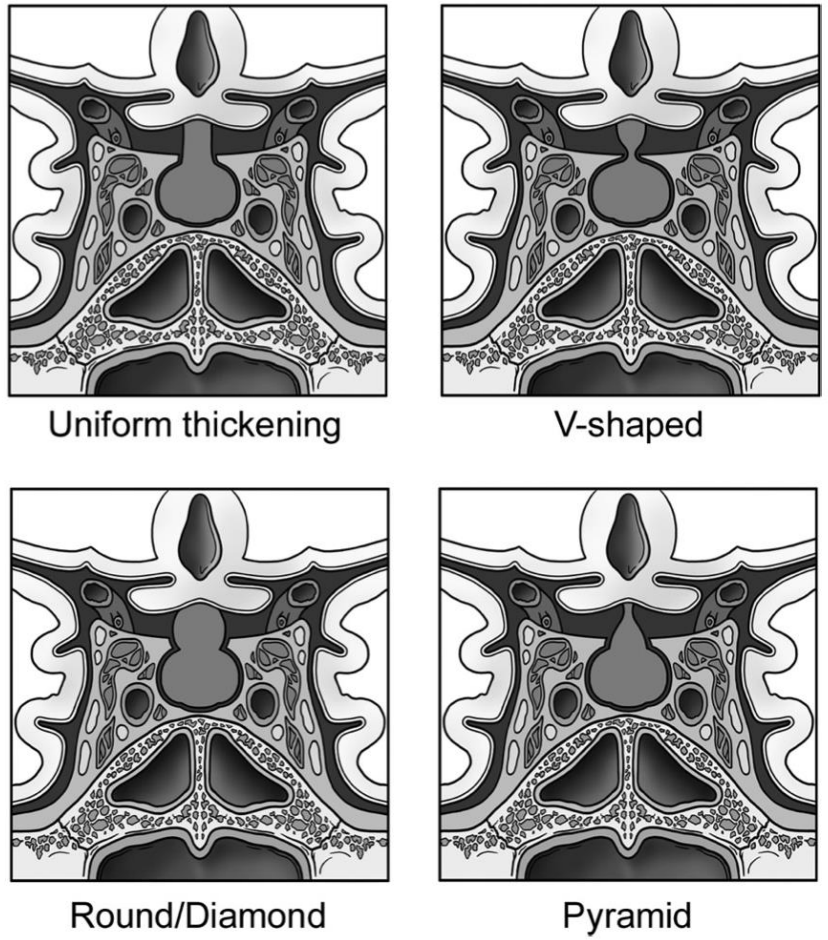
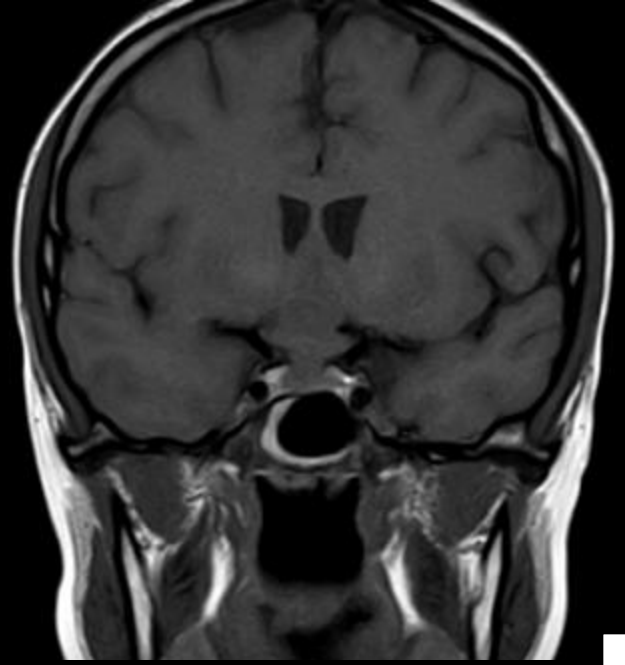


Image from Williams textbook of endocrinology 14th edition

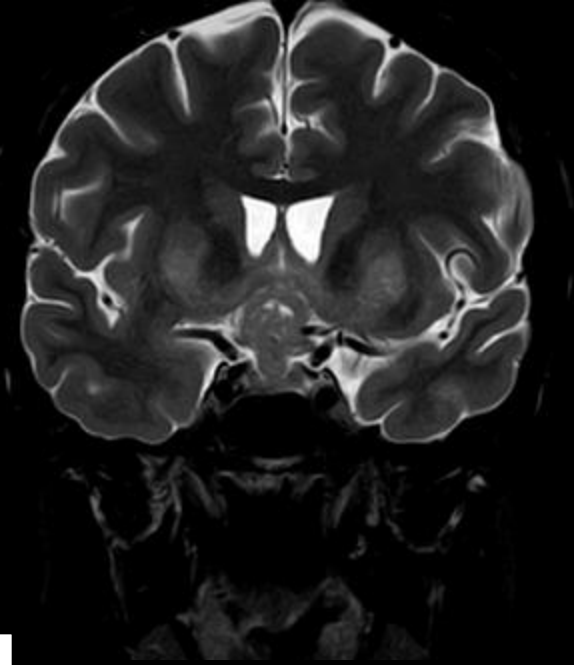
A 22-year-old female presented with amenorrhea for 1 year

She also had weight loss and nocturia.

- 8 AM cortisol 2 μg/dL
- FT4 0.5 ng/dL (0.8-1.8), TSH 4 uIU/mL (0.3-4.1)
- Prolactin 65 ng/mL (4.7-23.3)
- FSH 0.1 IU/L, LH <0.1 IU/L
- Estradiol < 18 pmol/L
- Urine sp.gr. 1.004
- β-hCG 74.2 mU/mL (0-5)
- α-fetoprotein 1.1 IU/mL (0-10)

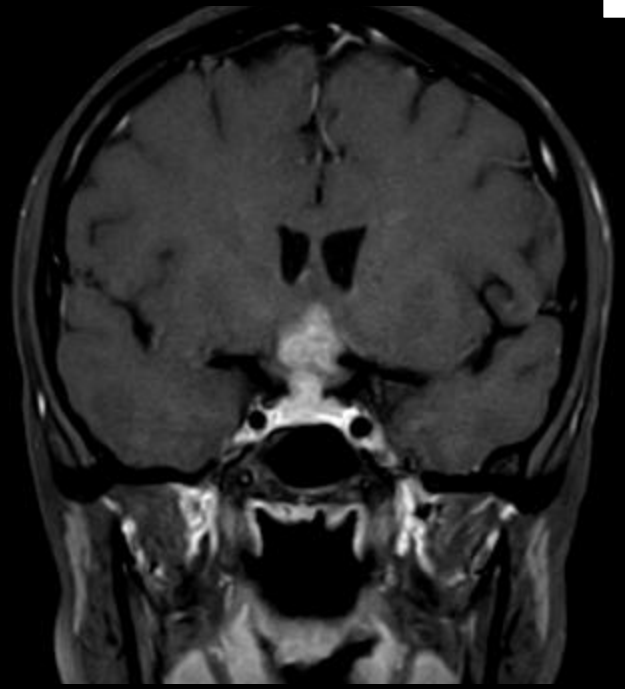


T1W

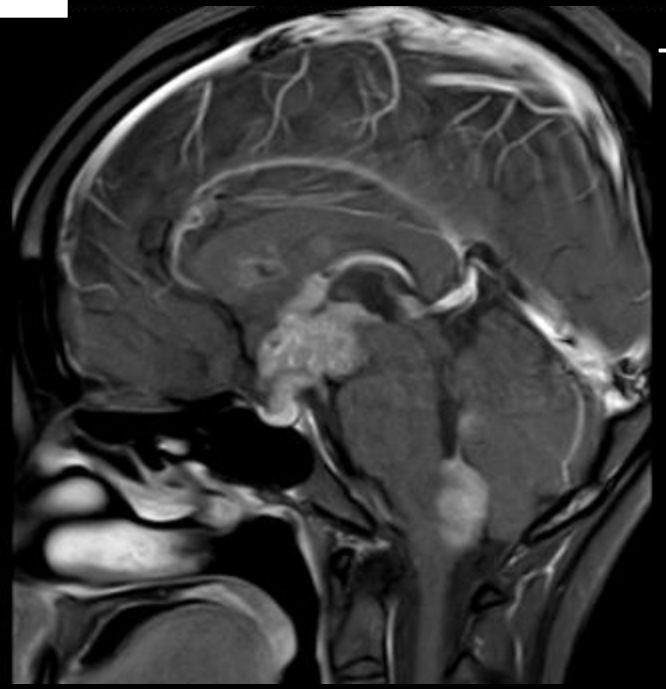


T2W

MRI pituitary



T1W + Gd



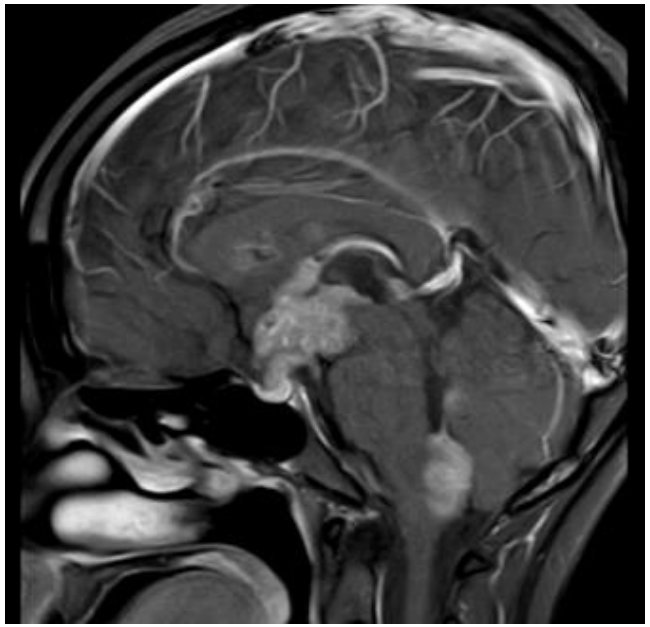
T1W + Gd

- Hormonal replacement
  - Glucocorticoids, thyroid hormone supplement and DDAVP
- Craniotomy with stalk biopsy
  - Findings: yellowish, soft, suckable tumor, moderately vascularized at sellar & suprasellar region
- Pathological result:
  - *Germinoma*

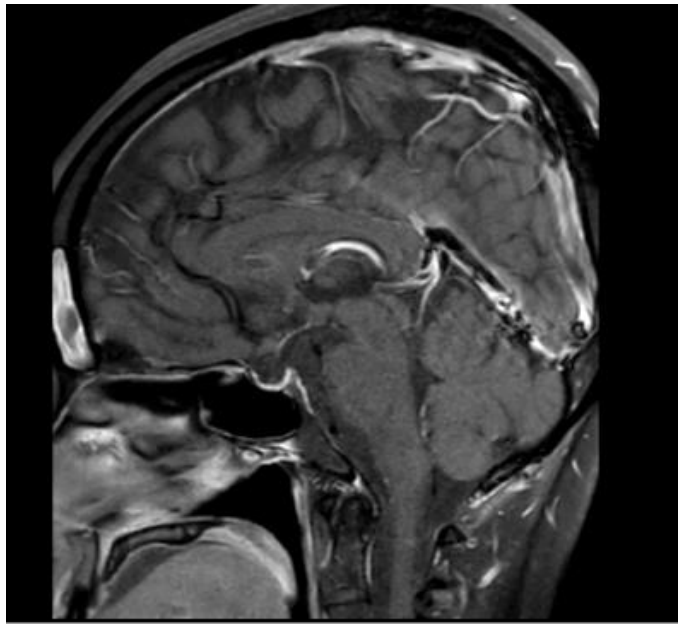
Intracranial Germ Cell Tumors

- Tumors may present as large compressive lesions or as a thickening of the pituitary stalk impinging on the optic chiasm →
  - Visual field defects
  - Hormonal deficiency
  - Diabetes insipidus
- Histological diagnosis is the mainstay of treatment.
  - Patients with elevated $\boldsymbol{\beta}$-hCG and/or $\boldsymbol{\alpha}$-fetoprotein can be treated without a biopsy.
- Prognosis is related to the histological subtype.

J Clin Endocrinol Metab 104: 3108–3123, 2019



5 years



Management:

- Chemotherapy (EP x 4)
- Radiotherapy
- Hormonal replacement

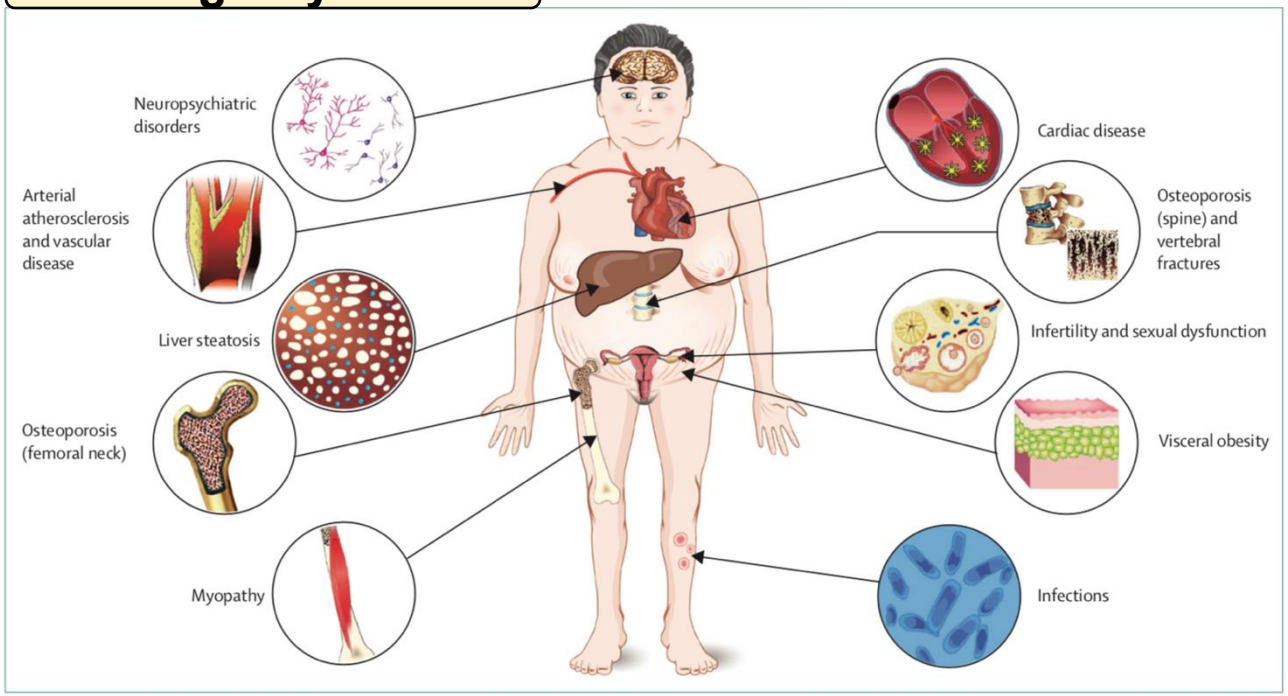
Treatment Hypopituitarism

- Specific
  - Depending on etiology

- Supportive
  - Hormonal replacement if indicated
    - Central adrenal insufficiency: glucococorticoid replacement (NO need for mineralocorticoid replacement), monitor clinical symptoms
    - Central hypothyroidism: LT4 and monitor FT4 (keep upper half of the reference range)
    - AVP deficiency: Desmopressin

Summary: Functioning Pituitary Tumors

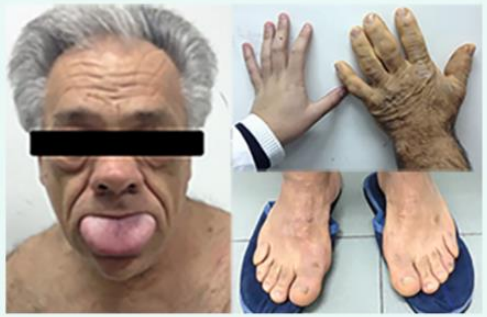
Cushing's syndrome



Acromegaly

Physical changes

- Prominence of the brow
- Prognatism
- Macroglossia
- Hyperhidrosis
- Enlargement of the nose and lips
- Soft-tissue hypertrophy
- Acral overgrowth



Cardiovascular complications

- Hypertension
- Biventricular hypertrophy
- Cardiomyopathy
- Congestive heart failure
- Arrhythmias
- Valve disease

Respiratory complications

- Upper airway obstruction
- Ventilatory dysfunction
- Sleep apnoea
- Excessive snoring

Metabolic and endocrine complications

- Impaired glucose tolerance
- Diabetes mellitus
- Insulin resistance
- Dyslipidaemia
- Thyroid goitre

Screening test for functional pituitary adenomas

Cushing's disease

- Dexamethasone suppression test
- 24-hr UFC
- Late night salivary cortisol

TSH-secreting tumor

- FT4, TSH

Acromegaly

- IGF-I

Prolactinoma

- PRL

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Lancet Diabetes Endocrinol (2016) 4: 611–29

Nat Rev Dis Primers. (2019) 5:20

Hypertension

ESC
European Society of Cardiology

European Heart Journal (2024) **45**, 3912–4018
https://doi.org/10.1093/eurheartj/ehae178

ESC GUIDELINES

2024 ESC Guidelines for the management of elevated blood pressure and hypertension

Developed by the task force on the management of elevated blood pressure and hypertension of the European Society of Cardiology (ESC) and *endorsed by the European Society of Endocrinology (ESE) and the European Stroke Organisation (ESO)*

McEvoy JW et al. Eur Heart J 2024. PMID: 39210715.

Screening Tests for Secondary Hypertension

Cause of secondary hypertension	Screening test
Primary aldosteronism	Aldosterone-to-renin ratio Helpful information can also be provided by reviewing prior potassium levels (hypokalaemia increases the likelihood of coexistent primary hyperaldosteronism)
Renovascular hypertension	Renal doppler ultrasound Abdominal CT angiogram or MRI
Phaeochromocytoma/paraganglioma	24 h urinary and/or plasma metanephrine and normetanephrine
Obstructive sleep apnoea syndrome	Overnight ambulatory polysomnography
Renal parenchymal disease	Plasma creatinine, sodium, and potassium eGFR Urine dipstick for blood and protein Urinary albumin-to-creatinine ratio Renal ultrasound
Cushing's syndrome	24 h urinary free cortisol Low-dose dexamethasone suppression test
Thyroid disease (hyper- or hypothyroidism)	TSH
Hyperparathyroidism	Parathyroid hormone Calcium and phosphate
Coarctation of the aorta	Echocardiogram Aortic CT angiogram

It's also not unusual for patients to never have hypokalemia. However, patients with more severe disease usually have hypokalemia or lower K levels.

Associated with Turner syndrome

CT, computed tomography; eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone.

McEvoy JW et al. Eur Heart J 2024. PMID: 39210715.

When to Screen for Secondary Hypertension

New-onset or uncontrolled hypertension in adults

- Drug-resistant/induced hypertension
- Abrupt onset of hypertension
- Onset of hypertension at <30 years old
- Exacerbation of previously controlled hypertension
- Disproportion of target organ damage for the degree of hypertension
- Accelerated/malignant hypertension
- Onset of diastolic hypertension in older adults (≥65 years old)
- Unprovoked or excessive hypokalemia

Screen of secondary hypertension

Target organ damage

- Coronary artery disease
- Cerebrovascular disease
- Hypertensive retinopathy
- LVH/dysfunction
- Heart failure
- Chronic kidney disease
- Albuminuria
- Peripheral artery disease

Whelton PK et al. J Am Coll Cardiol 2018. PMID: 29146535.

Table 10 Current definition of resistant hypertension

Definition of resistant hypertension
Hypertension is defined as resistant when a treatment strategy including appropriate lifestyle measures and treatment with maximum or maximally tolerated doses of a diuretic (thiazide or thiazide-like), a RAS blocker, and a calcium channel blocker fail to lower office systolic and diastolic BP values to <140 mmHg and/or <90 mmHg, respectively. These uncontrolled BP values must be confirmed by out-of-office BP measurements (HBPM or ABPM—*Section 5.1* for relevant BP thresholds).
Key considerations
• Resistant hypertension is not a disease, but an indicator that should be used to identify patients at high risk for CVD, in which secondary hypertension is also frequent; • Pseudo-resistant hypertension must be excluded, including that caused by non-adherence to treatment; • In patients with decreased eGFR (i.e. <30 mL/min/1.73 m^2) an adequately up-titrated loop diuretic is necessary to define resistant hypertension; • Patients with suspected resistant hypertension should be referred to specialized centres; • These ESC Guidelines do not include the terms 'controlled resistant hypertension' (BP at target but requiring ≥4 medications) or 'refractory hypertension' (BP not at target despite ≥5 medications).

Table 11 Conditions found to cause pseudo-resistance or resistance to blood pressure-lowering treatment

Causes of pseudo-resistant hypertension
Poor adherence to and persistence with treatment
White-coat phenomenon
Poor BP measurement method
Marked brachial artery calcification (Osler phenomenon)
Clinician inertia (inadequate doses, inappropriate combinations of BP-lowering drugs)
Munchausen syndrome (rare)
Causes of resistant hypertension
Behavioural factors
Overweight/obesity
Physical inactivity
Excess daily dietary sodium
Excess habitual alcohol consumption
Use of drugs or substances that may increase BP
See Supplementary data online, *Table S4*
Undetected secondary hypertension
See *Table 13*

BP, blood pressure.

McEvoy JW et al. Eur Heart J 2024. PMID: 39210715.

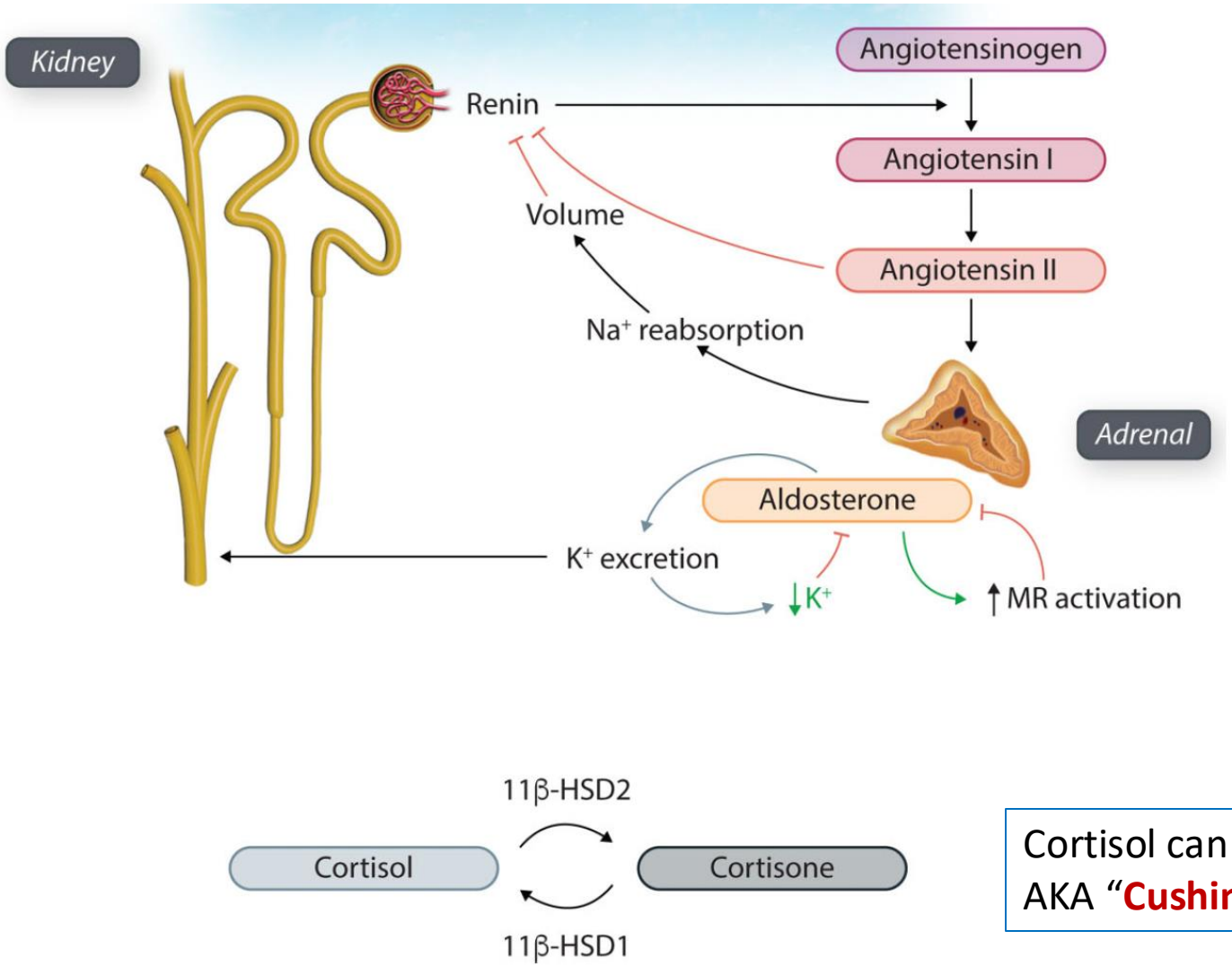
History Taking

- Age of onset รวมถึง BP แรกวินิจฉัย
- BP control & therapy adherence รวมไปถึงวิธีการวัด BP
  - นอกจากนี้ในผู้ป่วยบางรายที่คุม BP อยู่ดี ๆ BP คุมไม่ได้ก็ต้องหาว่ามีสาเหตุ
- Target organ damage เช่น เคยตรวจตาพบความผิดปกติ หรือ แพทย์เคยวินิจฉัยว่ามีหัวใจโต เคยมี HF ฯลฯ
- ประวัติ accelerated hypertension, hypertensive emergency รวมถึงเหตุกระตุ้นด้วย
- Alcohol/other drugs: cyclosporine A, VEGF inhibitors, NSAIDs, corticosteroids
- Family history: hereditary pheochromocytoma-paraganglioma, Glucocorticoid-remediable aldosteronism (GRA), Gordon syndrome ฯลฯ
- Others:
  - อาการอ่อนแรง น้ำหนักขึ้น เคยตรวจพบเกลือแร่ผิดปกติ หรือ น้ำตาลในเลือดสูง ประวัติประจำเดือนผิดปกติ (amenorrhea, PCOS) Cushing's syndrome
  - ประวัติ spells, paroxysm ท้องผูก น้ำหนักลด ประวัติ sudden death ในครอบครัว Pheochromocytoma
  - นอนกรน ง่วงนอนตอนกลางวัน หยุดหายใจ Obstructive sleep apnea
  - ประวัติ flash pulmonary edema, worsening renal function หลังได้ยา ACE inh, ARB Renal artery stenosis

Physical examination

- BP 4 extremities & orthostatic hypotension
- Pulse: Rates & rhythm
- General appearance & measurement: short stature, marfanoid habitus, obese, cushingoid appearance, acromegalic facies
- HEENT: neck circumference, mallampati, thyroid gland (size/consistency/nodule)
- Heart: JVP, heave/thrill/gallop/murmur, loud P2
- Skin: facial plethora, acanthosis nigricans, bruising, wide purplish striae, thin skin, hirsutism, café-au-lait spots, cutaneous lichen amyloidosis, vitiligo, onycholysis
- Eye ground: hypertensive retinopathy, retinal hemangioblastoma
- Neurological examination: proximal muscle weakness
- Bruits: carotid bruits, abdominal bruits

The Renin-angiotensin-aldosterone System



Assessing Aldosterone/Renin In Mineralocorticoid Hypertension

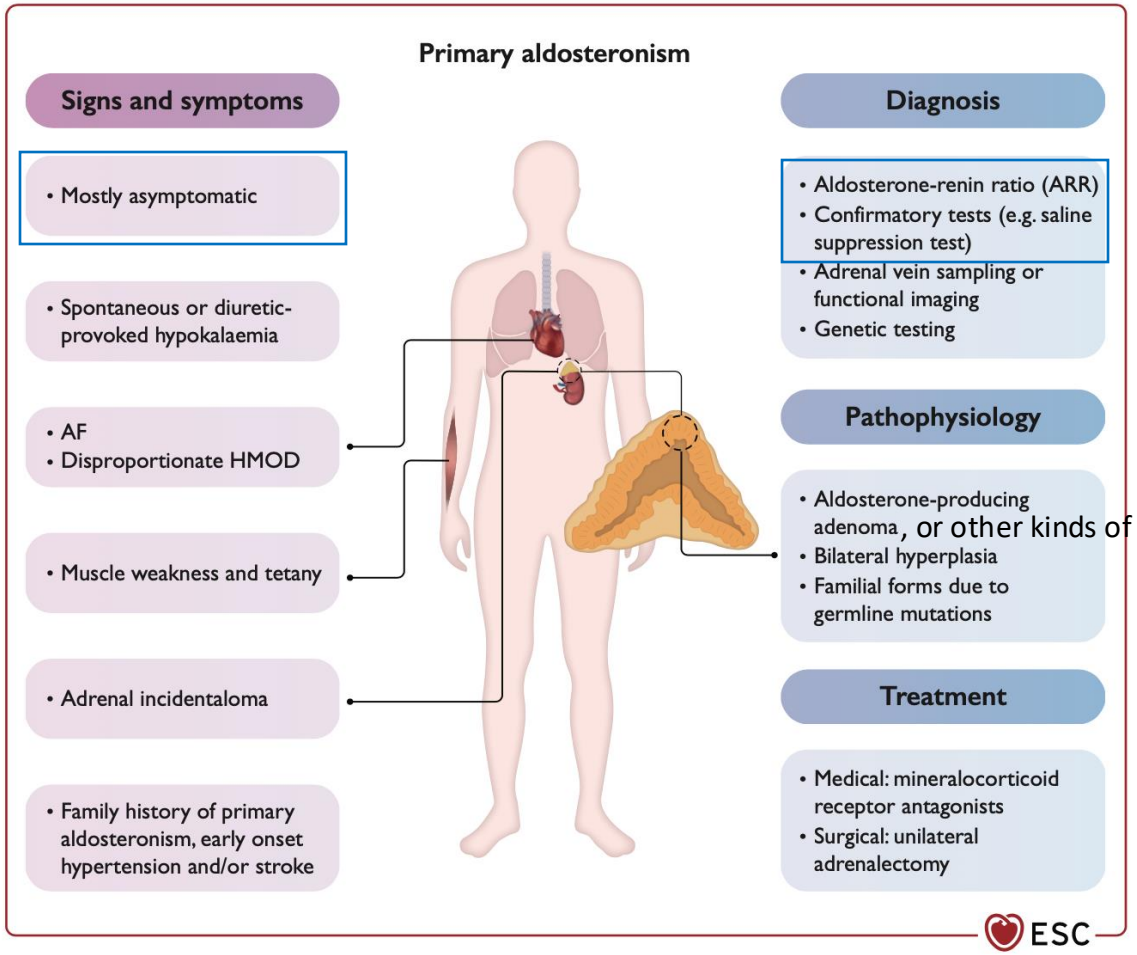
- **↑ Aldosterone, ↓Renin**
  - Primary Aldosteronism
    - Aldosterone-producing lesion in one or both adrenal glands
- **↑ Aldosterone, ↑Renin**
  - Secondary Aldosteronism
    - Pheochromocytoma, renal artery stenosis, reninoma (renin-producing tumor)
- **↓ Aldosterone, ↓Renin**
  - Something else causing MR activation
    - E.g., Cushing's syndrome, CAH

Cortisol can bind with MR in the presence of excess cortisol – AKA "**Cushing's Syndrome**." → ***Mineralocorticoid Hypertension***

MR, mineralocorticoid receptor; CAH, congenital adrenal hyperplasia

Image from Parksook WW, Williams GH. Cardiovasc Res 2023. PMID: 35388416.

Primary Aldosteronism



, or other kinds of aldosterone-producing lesions in one/both adrenal glands

McEvoy JW et al. Eur Heart J 2024. PMID: 39210715.

Health Impact of Primary Aldosteronism

Cardiovascular Risk

- Coronary artery disease
- ***Congestive heart failure***
- ***Left ventricular hypertrophy***
- ***Atrial fibrillation***
- ***Stroke***
- Cardiovascular mortality

Kidney Risk

- ***Glomerular hyperfiltration***
- Accelerated decline in glomerular filtration rate
- ***End-stage kidney disease***
- ***Proteinuria***

Metabolic Risk

- ***Type 2 diabetes mellitus***
- ***Metabolic syndrome/obesity***
- ***Obstructive sleep apnea***
- ***Osteoporosis/fractures***

Vaidya A et al. Am J Hypertens 2022. PMID: 35767459.

Who to Screen?

Groups with high prevalence of PA

- Blood pressure >150/100 mmHg, grade 2 and grade 3 hypertension
- Resistant hypertension
- Hypertension and spontaneous or diuretic-induced hypokalemia
- Hypertension and adrenal incidentaloma
- Hypertension and sleep apnea
- Hypertension and family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years)
- All first-degree relatives of patients with PA

Endocrine Society 2016

All hypertensives – Japan guidelines 2021

Atrial fibrillation – European Guidelines 2020

All hypertensives – ESC 2024

Funder JW et al. J Clin Endocrinol Metab 2016. PMID: 26934393
Mulatero P et al. J Hypertens 2020. PMID: 32890264
Naruse M et al. Endocr J 2022. PMID: 35418526.

Algorithm for Primary Aldosteronism Management According to the Endocrine Society Guideline 2016

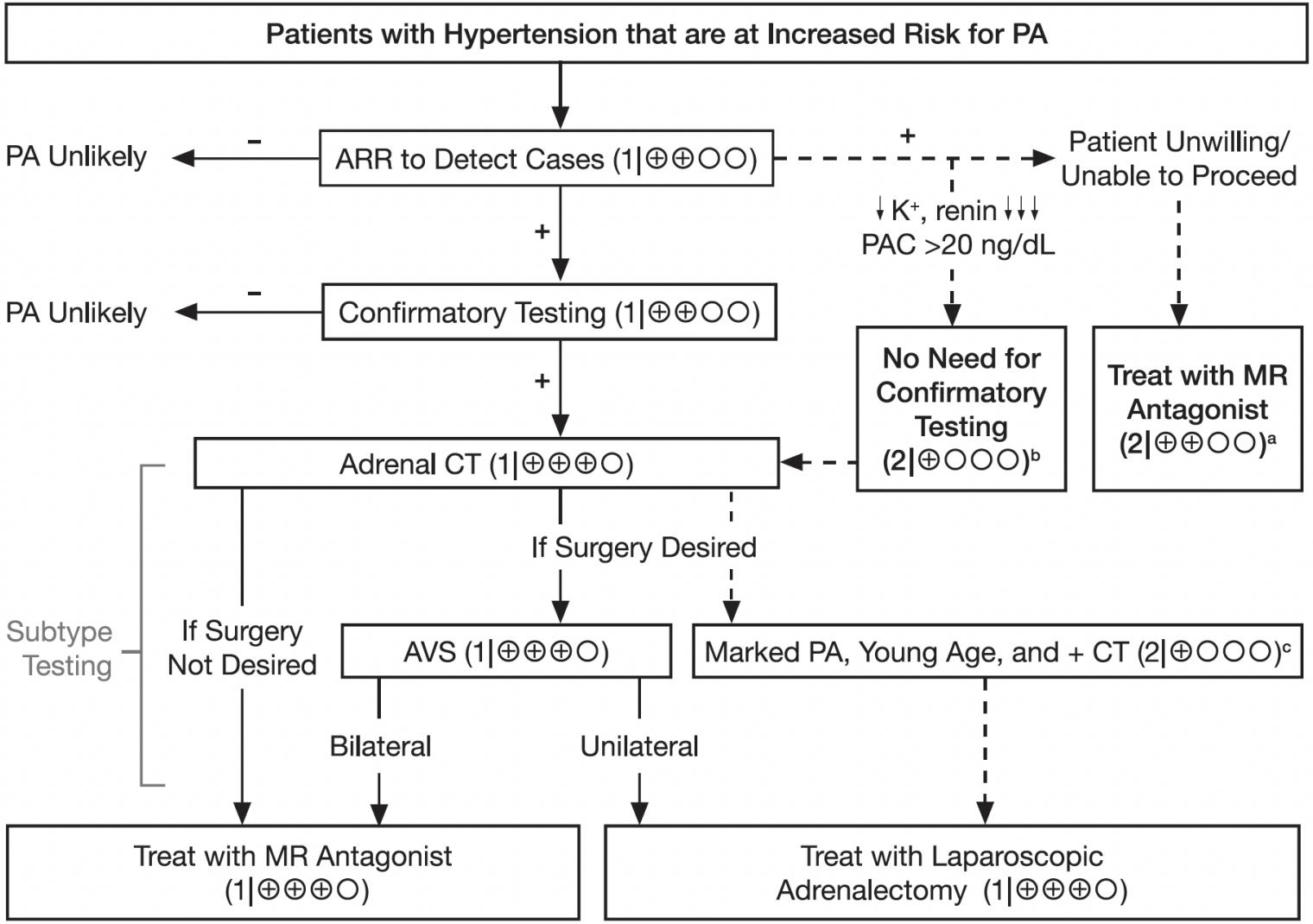
Who to screen?

How to screen?

Confirmatory testing

Subtyping

Treatment



Images from Funder JW et al. J Clin Endocrinol Metab 2016. PMID: 26934393

How to Screen for Primary Aldosteronism?

- Aldosterone-to-renin ratio (ARR)

- Aldosterone and renin values should also be evaluated independently rather than relying on the ARR alone.

เพราะถ้า renin ต่ำมาก เอามาหารยังไง ARR ก็จะสูงได้
เช่น Aldosterone = 5 ng/dL, PRA = 0.1 ng/mL/h
→ ARR = 50 ng/dL per ng/mL/h

Factors Affecting the Interpretation of the Screening Test

Factors	Ideal condition
Medication	Withdraw antihypertensive medications that affect ARR
Potassium levels	Normokalemia
Posture	Upright
Sodium intake	Liberalized sodium diet
Timing	Mid morning, up for at least 2 hours, seated for 5-15 minutes

Antihypertensive agents with minimal effects on aldosterone levels: verapamil slow-release, hydralazine, doxazosin

Funder JW et al. J Clin Endocrinol Metab 2016. PMID: 26934393

Drugs and Conditions and their effects on aldosterone, renin, ARR.

Factor	Effect on plasma aldosterone levels	Effect on renin levels	Effect on ARR
Serum potassium status			
Hypokalaemia	↓	→↑	↓ **(FN)**
Potassium loading	↑	→↓	↑
Sodium restriction	↑	↑↑	↓ **(FN)**
Sodium loading	↓	↓↓	↑ **(FP)**
Drugs			
Beta-adrenergic blockers	↓	↓↓	↑ **(FP)**
Calcium channel blockers (DHPs)	→↓	→↑	→↓ **(FN** with short-acting DHPs**)**
ACE inhibitors	↓	↑↑	↓ **(FN)**
ARBs	↓	↑↑	↓ **(FN)**
Potassium-sparing diuretics	↑	↑↑	↓ **(FN)**
Potassium-wasting diuretics	→↑	↑↑	↓ **(FN)**
Alpha-2 agonists (clonidine, methyldopa)	↓	↓↓	↑ **(FP)**
NSAIDs	↓	↓↓	↑ **(FP)**
Steroids	↓	→↓	↑ **(FP)**
Contraceptive agents (drospirenone)	↑	↑	↑ **(FP)**

↑, raised; ↓, lowered; →, no effect; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARR, aldosterone-to-renin ratio; DHPs, dihydropyridines; FN, false negative; FP, false positive; NSAID, non-steroidal anti-inflammatory drug.

McEvoy JW et al. Eur Heart J 2024. PMID: 39210715.

Interpretation of Screening Results

	ARR, ng/dL per ng/mL/h	Serum Aldosterone, ng/dL	Plasma Renin Activity, ng/mL/h
Most conservative	≥40	≥20	≤0.50
Conservative	≥30	≥15	≤1.0
More permissive	≥20 or ≥25	≥9-10	≤1.0
Most permissive	≥20	≥6	≤0.50

ARR, aldosterone-to-renin ratio

Adapted from Vaidya A et al. Endocr Rev 2018. PMID: 30124805.

Confirmatory Testing

- Patients with a positive ARR are recommended to undergo one or more confirmatory tests to definitively confirm or exclude the diagnosis.

- However, in the setting of ***spontaneous hypokalemia, plasma renin below detection levels, plus PAC >20 ng/dL,***
  - There may be no need for further confirmatory testing.

ARR, aldosterone-to-renin ratio;
PAC, plasma aldosterone concentration

Funder JW et al. J Clin Endocrinol Metab 2016. PMID: 26934393

Confirmatory Testing

- Saline infusion test
- Captopril challenge test
- Oral sodium loading test
- Fludrocortisone suppression test

การทำ test	Interpretation	Remarks
SIT Patients stay in the recumbent position for at least 1 h before and during the infusion of 2 L of 0.9% saline iv over 4 h, starting at 8–9.30 AM. Blood samples for renin, aldosterone, cortisol, and plasma potassium are drawn at time zero and after 4 h, with BP and heart rate monitored throughout the test. In a modified approach, which appears (in preliminary studies) to have much higher sensitivity for diagnosing PA, patients remain in a seated position for at least 30 min and during the infusion (73).	Postinfusion plasma aldosterone levels <5 ng/dL (140 pmol/L) make the diagnosis of PA unlikely, whereas levels >10 ng/dL (280 nmol/L) are a sign of very probable PA. Values between 5 and 10 ng/dL are indeterminate, although a cutoff of 6.8 ng/dL (190 pmol/L) has been found to offer the best trade-off between sensitivity and specificity (57, 58, 224, 225). For the seated SIT, a postinfusion plasma aldosterone of >6 ng/dL (170 pmol/L) confirms PA, provided plasma cortisol concentration is lower than the value obtained basally (to exclude a confounding ACTH effect) (73).	This test should not be performed in patients with severe uncontrolled hypertension, renal insufficiency, cardiac arrhythmia, or severe hypokalemia.
Captopril challenge test Patients receive 25–50 mg of captopril orally after sitting or standing for at least 1 h. Blood samples are drawn for measurement of PRA, plasma aldosterone, and cortisol at time zero and at 1 or 2 h after challenge, with the patient remaining seated during this period.	Plasma aldosterone is normally suppressed by captopril (>30%). In patients with PA it remains elevated and PRA remains suppressed (58, 60, 163, 227). Differences may be seen between patients with APA and those with IAH, in that some decrease of aldosterone levels is occasionally seen in IAH (228).	There are reports of a substantial number of false-negative or equivocal results (59, 229).

Funder JW et al. J Clin Endocrinol Metab 2016. PMID: 26934393

Subtyping in Primary Aldosteronism

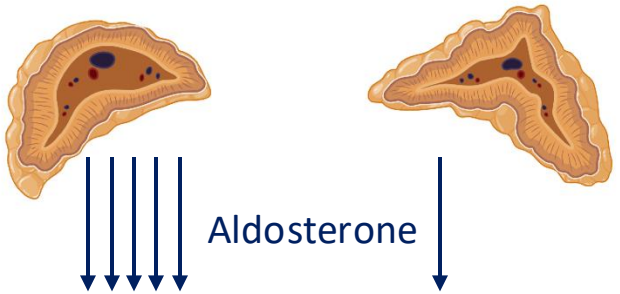
- Purpose: to classify between lateralizing (known as unilateral) v.s. non-lateralizing PA (or bilateral)
- Modalities
  - Cross-sectional imaging
  - Adrenal venous sampling

Benefits from curative adrenalectomy

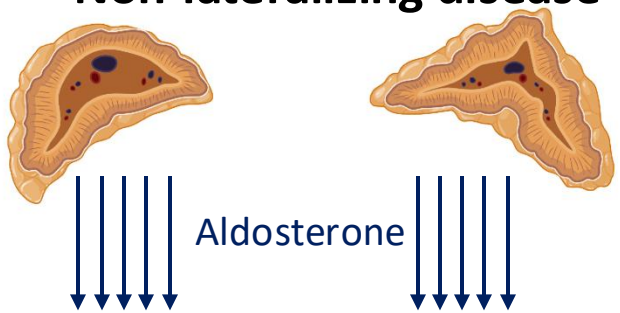
In patients ***<35 years*** with ***marked PA*** (e.g., spontaneous hypokalemia; PAC >30 ng/dL) and ***solitary unilateral apparent adenoma on CT scan***, a case can be made to proceed directly to unilateral adrenalectomy without prior AVS.

Endocrine Society 2016

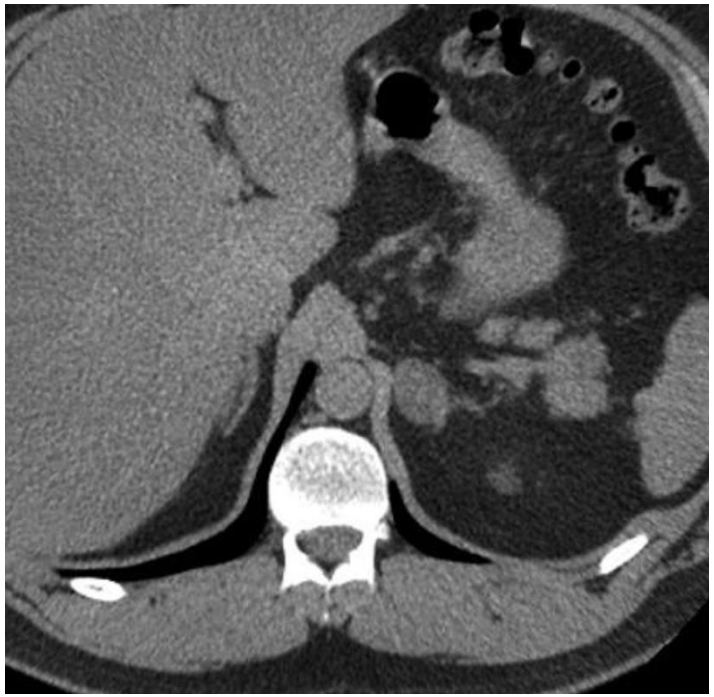
Lateralizing disease



Non-lateralizing disease



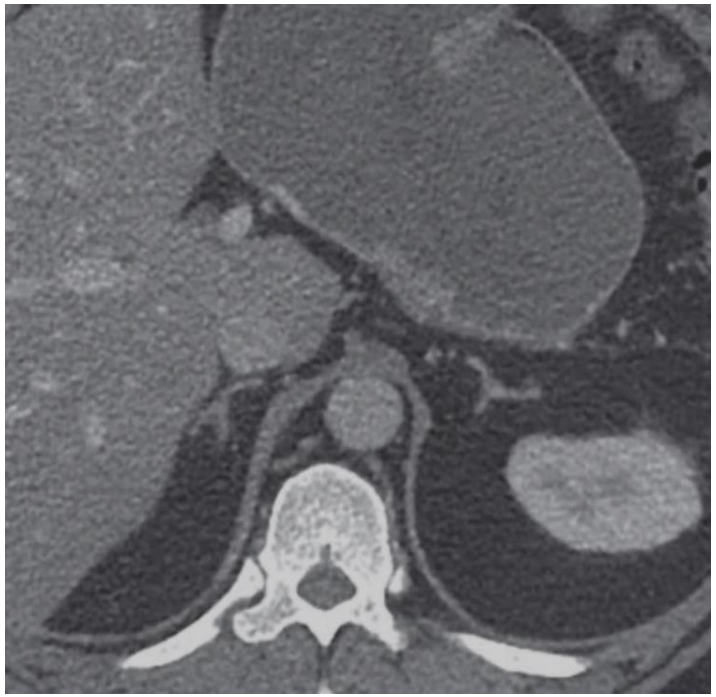
30-year-old patient, hypertension & hypoK
PAC = 50 ng/dL, PRA 0.4 ng/mL/h



Unilateral left adrenal adenoma

May skip AVS and proceed to left unilateral adrenalectomy

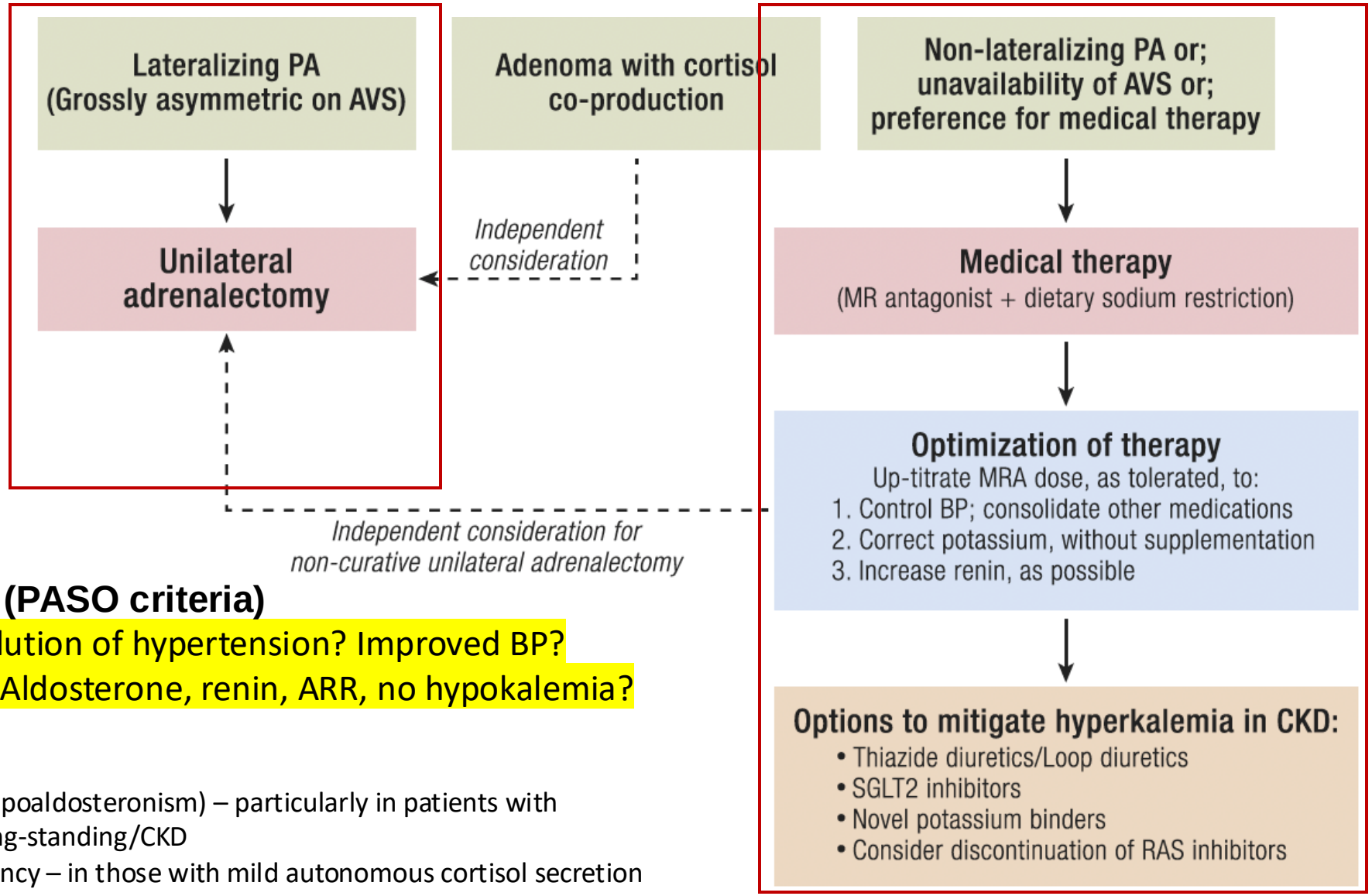
30-year-old patient, hypertension & hypoK
PAC = 50 ng/dL, PRA 0.4 ng/mL/h



Normal-appearing adrenal glands

AVS is necessary if surgery is desired

Treatment in Primary Aldosteronism



Postoperative (PASO criteria)

- **Clinical:** Resolution of hypertension? Improved BP?
- **Biochemical:** Aldosterone, renin, ARR, no hypokalemia?

Other considerations

- Hyperkalemia (hypoaldosteronism) – particularly in patients with advanced age/long-standing/CKD
- Adrenal insufficiency – in those with mild autonomous cortisol secretion

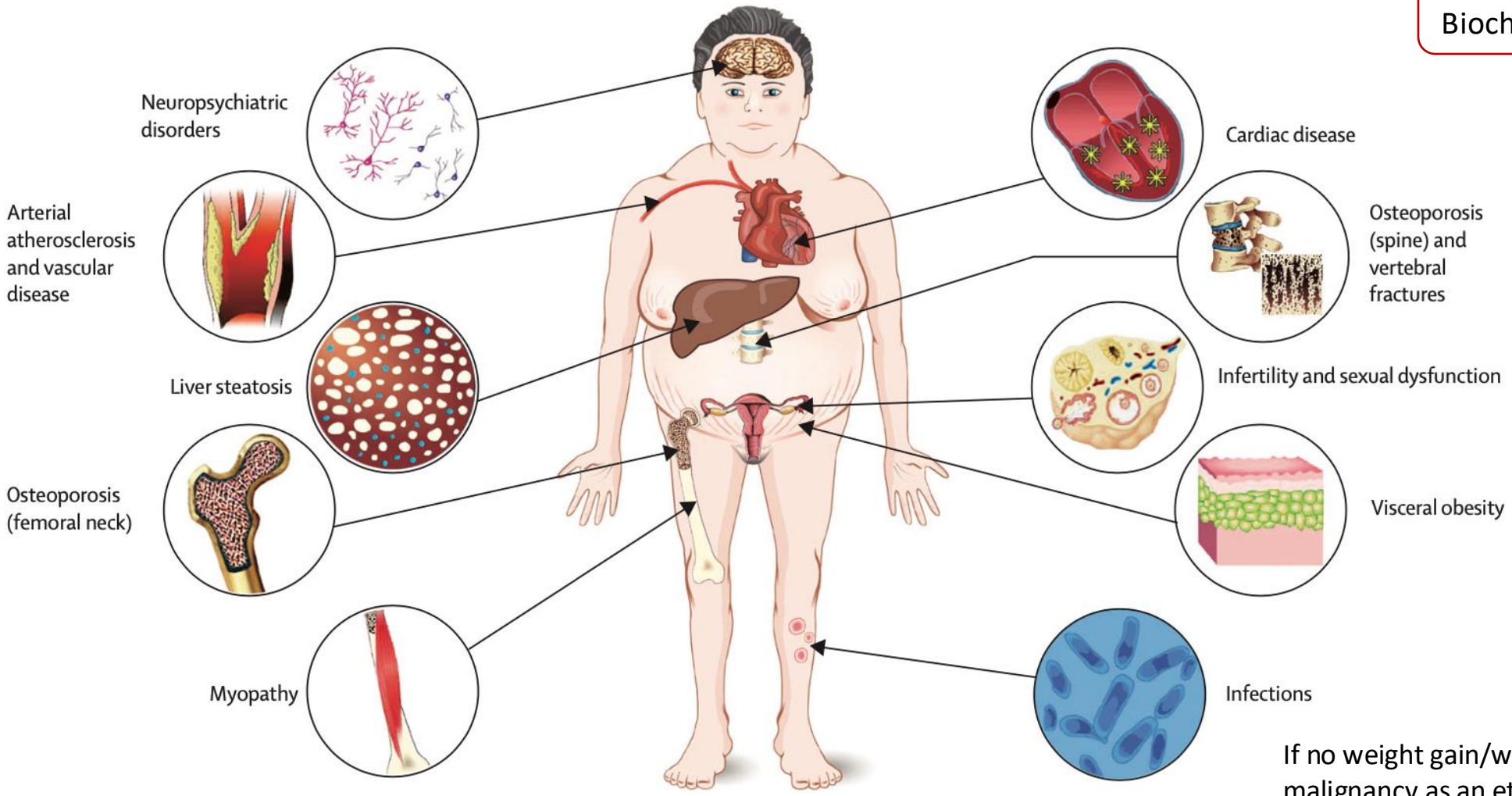
Image from Hundemer GL et al. Endocr Rev 2023. PMID: 37439256.

Cushing's Syndrome

Appearance: Cushing's
Biochemical profile: central AI

Etiology

- Exogenous Cushing's
- ACTH-dependent Cushing's syndrome
- ACTH-independent Cushing's syndrome

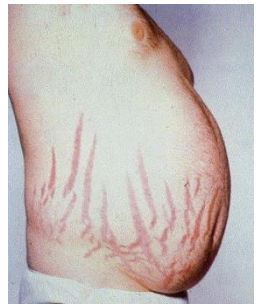


If no weight gain/weight loss→ may suggest malignancy as an etiology

History taking - Onset, hypertension (or worsening hypertension), hyperglycemia/DM, weight gain, secondary amenorrhea, infection, fracture, thromboembolism, muscle weakness, psychiatric disorders

Image from Pivonello R et al. Lancet Diabetes Endocrinol 2016. PMID: 27177728.

Symptoms	Signs	Overlapping conditions
Features that best discriminate Cushing's syndrome; most do not have a high sensitivity		
	Easy bruising	
	Facial plethora	
	Proximal myopathy (or proximal muscle weakness)	
	Striae (especially if reddish purple and > 1 cm wide)	
	In children, weight gain with decreasing growth velocity	
Cushing's syndrome features in the general population that are common and/or less discriminatory		
Depression	Dorsocervical fat pad ("buffalo hump")	Hypertension[b]
Fatigue	Facial fullness	Incidental adrenal mass
Weight gain	Obesity	Vertebral osteoporosis[b]
Back pain	Supraclavicular fullness	Polycystic ovary syndrome
Changes in appetite	Thin skin[b]	Type 2 diabetes[b]
Decreased concentration	Peripheral edema	Hypokalemia
Decreased libido	Acne	Kidney stones
Impaired memory (especially short term)	Hirsutism or female balding	Unusual infections
Insomnia	Poor skin healing	
Irritability		



Purplish striae

Nieman LK et al. J Clin Endocrinol Metab 2008. PMID: 18334580.
Image from https://doi.org/10.1016/j.clindermatol.2006.04.012

History Taking & Physical Examination

History

- ☐ Changes in appetite
- ☐ Weight gain
- ☐ Back pain
- ☐ Menstrual abnormalities
- ☐ Decreased libido
- ☐ Back pain
- ☐ Depression
- ☐ Fatique
- ☐ Impaired memory
- ☐ Insomnia
- ☐ Irritability

Concomitant medication

- ☐ OCPs
- ☐ exogenous steroid

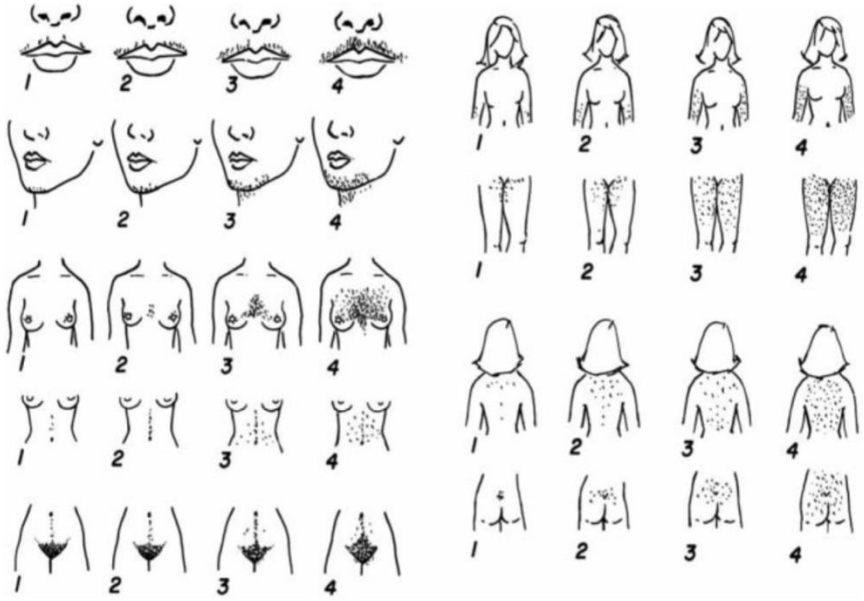
Physical examination:

- SBP……mmHg
- DBP……mmHg
- Height…….cm
- Weight…….kg
- BMI…….kg/m^2
- Waist-to-hip ratio……

- ☐ Easy bruising
- ☐ Facial plethora
- ☐ Striae
- ☐ Proximal myopathy
- ☐ Acne
- ☐ Hirsutism
- ☐ Thin skin
- ☐ Dorsocervical fat pad
- ☐ Facial fullness
- ☐ Poor skin healing
- ☐ Supraclavicular fullness
- ☐ Hyperpigmentation
- ☐ Peripheral edema
- ☐ Central obesity

CO-MORBIDITIES

- ☐ Diabetes mellitus/onset(months)….
- ☐ Hypokalemia
- ☐ Incidental adrenal mass
- ☐ Infection
- ☐ Hypertension/onset…
- ☐ Vertebral osteoporosis/onset…
- ☐ Kidney stones/onset…
- ☐ Dyslipidemia/onset…
- ☐ Obesity
- ☐ PCOS



Ferriman Gallwey Scoring System

Hirsutism Endocrine Society Guideline 2011

Etiology of Endogenous Cushing's Syndrome

	Proportion (%)	Age (peak)	Female:male	Features
ACTH-dependent	70–80	..	..	..
Cushing's disease	60–70	..	..	..
Corticotroph adenoma	60–70	3rd–4th decades	3–5:1	Roughly 50% non-visible on MRI
Corticotroph hyperplasia	Very rare	..	..	..
Ectopic ACTH*	5–10	..	..	..
Malignant neuroendocrine tumours	About 4	5th–6th decades	0·6–1:1	Might have very high ACTH
Benign neuroendocrine tumours	About 6	3rd–4th decades	..	Might respond to dexamethasone, CRH, desmopressin
Occult neuroendocrine tumours	About 2	..	..	..
Ectopic CRH	Very rare	..	..	Causes pituitary corticotroph hyperplasia
ACTH-independent	20–30	..	..	..
Unilateral adrenal	..	..	..	..
Adenoma	10–22	4th–5th decades	4–8:1	Most pure cortisol secretion
Carcinoma	5–7	1st, 5th–6th decades	1·5–3:1	Mixed cortisol and androgen frequent
Bilateral adrenal	1–2	..	..	..
Bilateral macronodular adrenal hyperplasia†	<2	5th–6th decades	2–3:1	Modest cortisol secretion compared with size; raised steroid precursors; might have combined androgen and mineralocorticoid cosecretion
Aberrant G-protein-coupled receptors	..	..	..	..
Autocrine ACTH production	..	..	..	..
Sporadic or familial (*ARMC5*)	..	..	..	..
Bilateral micronodular adrenal hyperplasias	<2	..	..	Adrenal size often normal
Primary pigmented nodular adrenocortical disease	Rare	1st–3rd decades	0·5:1 <12 years 2:1 >12 years	Frequent paradoxical increase of urine free cortisol with Liddle's oral dexamethasone suppression test
Isolated or familial with Carney complex	Rare	1st–3rd decades	..	..
Isolated micronodular adrenocortical disease	Very rare	Infants	..	Non-pigmented adrenal micronodules
Primary bimorphic adrenocortical disease	Very rare	Infants	..	..
McCune-Albright syndrome	Rare	Infants (<6 months)	1:1	Internodular adrenal atrophy
Bilateral adenomas or carcinomas	Rare	4th–5th decades	2–4:1	..

ACTH=adrenocorticotropic hormone. CRH=corticotropin-releasing hormone. *Most frequent sources of ectopic ACTH syndromes are small cell lung carcinoma and neuroendocrine tumours of lung, thymus, and pancreas. Less frequent causes include medullary thyroid carcinoma, gastrinoma, phaeochromocytoma, prostate carcinoma, and several others. †In bilateral macronodular adrenal hyperplasia tissues, autocrine and paracrine ACTH might be produced and contribute to cortisol secretion. If confirmed by in-vivo studies, the ACTH-independent classification will need to be modified in the future.

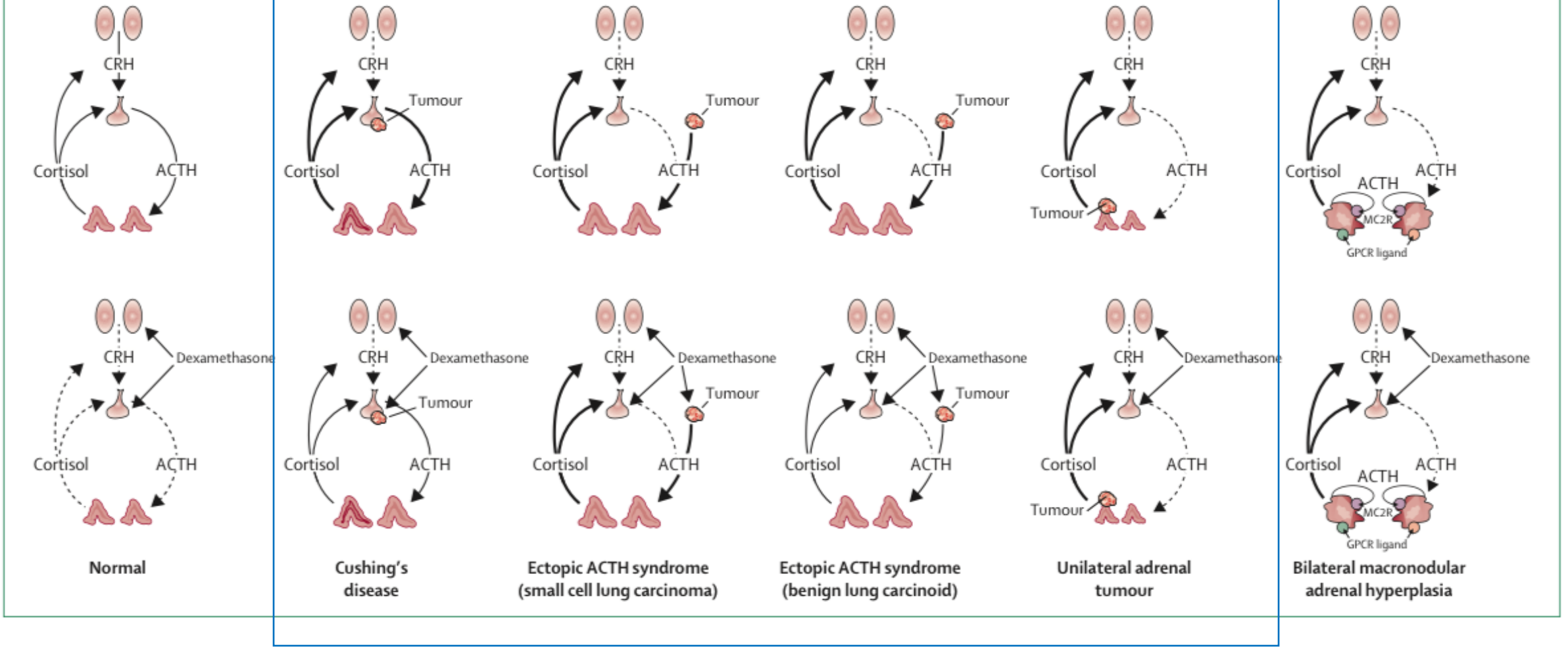
***Table 1*: Causes of endogenous Cushing's syndrome**

ในกลุ่ม malignancy e.g., ectopic ACTH ผู้ป่วยอาจจะไม่มี Cushingoid appearance แต่มาด้วยอาการเด่นทาง metabolic เช่น hypertension, hypoK, hyperglycemia

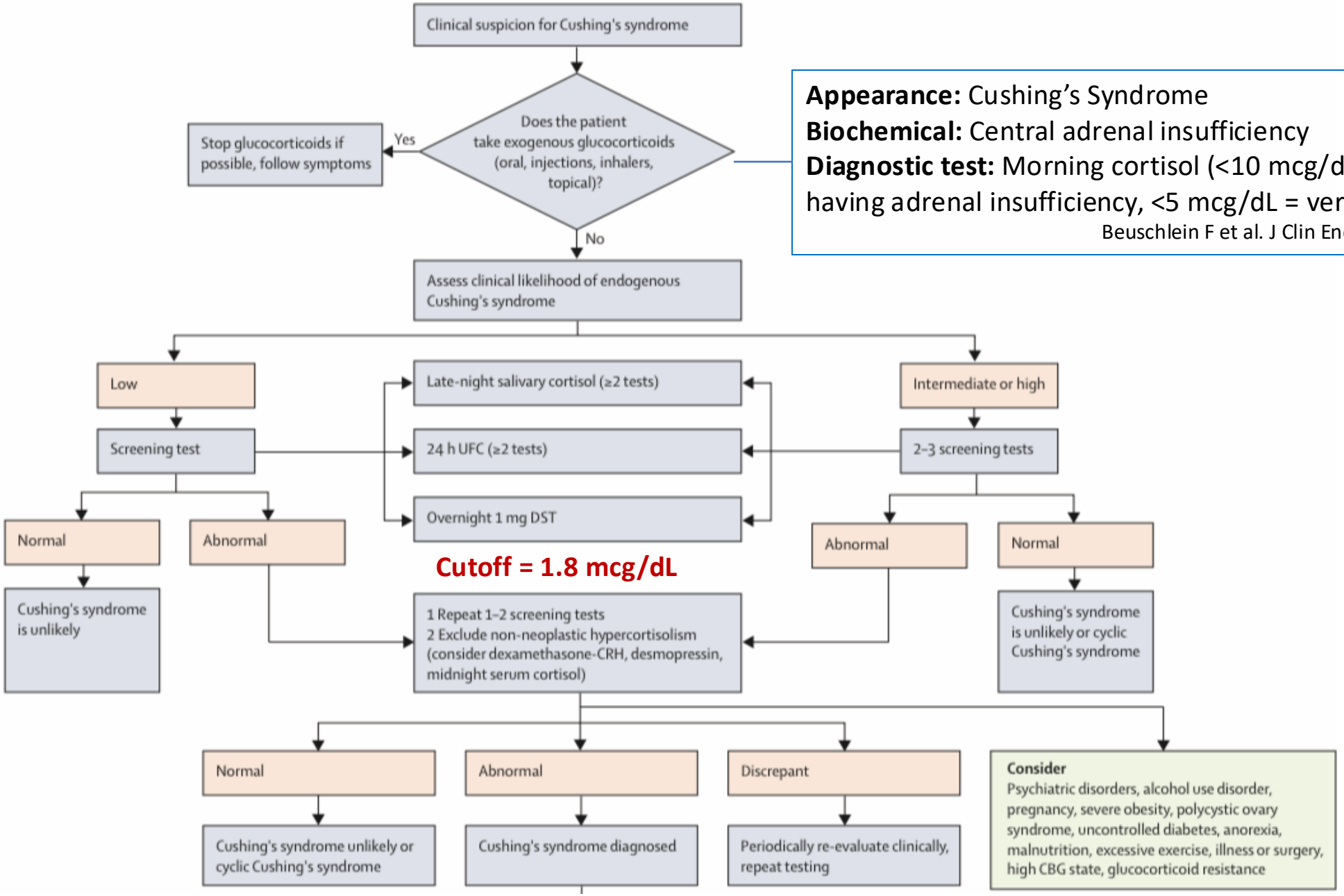
In females,
PE: hirsutism, virilization

Cushing's syndrome ที่น้ำหนักไม่ขึ้น
- คิดถึง malignancy มากขึ้น

Lacroix A et al. Lancet 2015. PMID: 26004339.



Lacroix A et al. Lancet 2015. PMID: 26004339.



Appearance: Cushing's Syndrome
Biochemical: Central adrenal insufficiency
Diagnostic test: Morning cortisol (<10 mcg/dL increased the likelihood of having adrenal insufficiency, <5 mcg/dL = very high likelihood)

Beuschlein F et al. J Clin Endocrinol Metab 2024. PMID: 38724043.

Image from Fleseriu M et al. Lancet Diabetes Endocrinol 2021. PMID: 34687601.

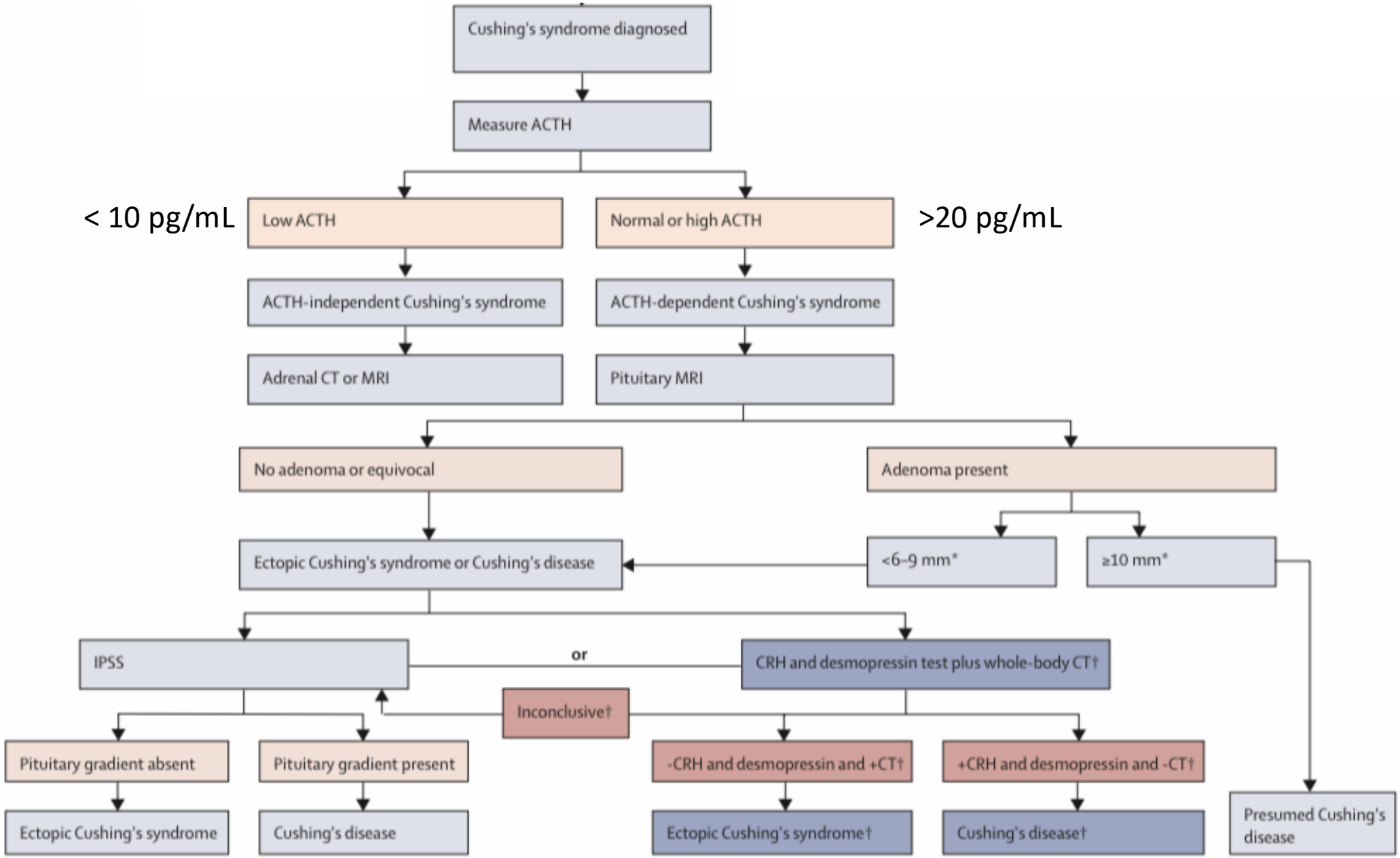


Image from Fleseriu M et al. Lancet Diabetes Endocrinol 2021. PMID: 34687601.

✍️Cushing's syndrome เป็นกลุ่มอาการที่เกิดจาก glucocorticoid เกินในร่างกายเป็นเวลานาน
โดย glucocorticoid จะส่งผลต่อทุกระบบในร่างกายตั้งแต่หัวจรดเท้า ดังอาการทั้งหมดที่แสดงในรูปที่ 1 ครับ
เมื่อดูรูปที่ 1 กรอบล่างๆจะเห็นว่ามีอาการและอาการแสดงบางอย่างพบได้ในคนทั่วไป โรคอ้วน หรือ คนไข้โรคอื่นๆได้ เช่น อ่อนเพลีย น้ำหนักขึ้น ความจำไม่ค่อยดี ซึมเศร้า ฯลฯ
แต่อาการในกรอบแดงคือสิ่งที่ต้องจำให้ได้ เพราะเป็นอาการที่พบในโรคอื่นๆได้น้อย เรียกว่า "best discriminate Cushing's syndrome" ได้แก่ จ้ำเลือดง่าย หน้าแดง 👹 กล้ามเนื้อส่วนต้นอ่อนแรง รอยแตกม่วง (มากกว่า 1 cm.) เคสที่เอามาสอบ Cushing's syndrome ระดับ resident น่าจะต้องมี signs พวกนี้ครับ

.

✍️ขั้นตอนการ work up เมื่อสงสัย Cushing's syndrome ค่อยไปทีละขั้นนะคับ ไม่ข้ามขั้น

1️⃣ ขั้นตอน 1 ถามประวัติยา เพื่อแยก exogenous Cushing's syndrome ออกไปก่อน ไม่ได้ถามแค่ยากิน💊นะครับ 💉ยาฉีดเข้าข้อ ฉีดเข้ากล้าม ยาทา ยาพ่น สวนก้น ฯลฯ ต้องถามให้หมด
ถามว่าใช้ยานั้นรักษาโรคอะไร ลักษณะยาเป็นยังไง (ยาเม็ด ผง ใบสมุนไพร ลูกกลอน ฯลฯ) ช่วงที่ได้ยาอาการเป็นไง ไม่ได้ยาแล้วเป็นไง หยุดยาไปแล้วนานเท่าไหร่ ฯลฯ
ถ้ามียาสงสัย ให้หยุดยา 7 วัน เจาะ 8am cortisol ถ้าค่า < 3 ug/dl วินิจฉัยเลยว่ามีภาวะ adrenal insufficiency จาก exogenous steroid (secondary adrenal insufficiency)

2️⃣ ขั้นตอน2 ตรวจเพื่อยืนยันภาวะ glucocorticoid excess ดูรูปที่ 2 ประกอบกัน สิ่งสำคัญในขั้นตอนนี้ คือ การเลือกtest ให้เหมาะสมกับคนไข้ อ่านดีดีนะครับ

.

*** ต้องระวังภาวะ pseudo Cushing ดูในรูป 3 ครับ ท่องง่ายๆ "อ้วน เศร้า เหล้า ท้อง poor controlled DM" ต้องเลือก test ที่จำเพาะกับภาวะนั้นๆครับ ***

.

👉UFC (ตรวจอย่างน้อย 2 ครั้ง)

✔️ใช้ใน คนที่มีการกวน CBG เพราะวัด free cortisol จาก urine
Pregnancy, คนที่ทำงานเป็นกะ

❌ไม่ใช้ใน
GFR< 60
กินน้ำมากกว่า 5 ลิตรต่อวัน
คนที่ใช้ยาที่กวนการตรวจ เช่น carbamazepine, fenofibrate (วิธี HPLC), ยาที่ยับยั้ง enzyme 11- beta HSD2 เช่น licorice, carbenoxolone

.

.

👉1 mg overnight DST, 2 day low dose DST
ทำง่ายแต่ข้อจำกัดเยอะ

✔️ใช้ใน เฉพาะ 2 day low dose DST ใช้ใน pseudoCushing พวก psychiatric conditions, morbid obesity, DM, alcoholism

❌ไม่ใช้ใน
คนที่มี CBG เปลี่ยนแปลง เช่น กิน estrogen (ต้องหยุด 6 สัปดาห์) nephrotic syndrome (CBG ต่ำ)
คนที่ใช้ยาที่กวน dexamethasone metabolism ดังรูป 2 นะครับ เช่น ใช้ยาที่เร่ง dexamethasone metabolism ทำให้ค่า cortisol สูงกว่าความเป็นจริง (falsely high) คือกลุ่ม ยากันชัก, rifampicin เป็นต้น

.

.

👉Late night salivary cortisol (ตรวจอย่างน้อย 2 ครั้ง)
ในประเทศไทยยังไม่แพร่หลาย

✔️ใช้ใน คนที่มีการกวน CBG เพราะวัด free form

❌ ไม่ใช้ใน กิน licorice (ต้องไปอ่านเรื่องชะเอมในวงราวน์นะครับ) chewing tobacco ใช้ steroid ป้ายปาก
ระวังเก็บเลือดปนน้ำลาย

Other Laboratory Investigations

LABORATORY INVESTIGATIONS

- FPG……
- HbA1c…….
- Cr……
- Na…….
- K…….
- Cl……
- HCO3……..
- Hb……..
- Hct…….
- Platelet……..
- WBC……
- TC……..
- TG…….
- LDL……
- HDL……..

DIAGNOSTIC LABORATORY

- 1mg DST…….
- UFC……
- Midnight salivary cortisol…….
- ACTH……
- HDDST……
- BMD L-spine……..
- BMD Hip……
- BMD FN……

OTHERS

□ IPSS □ DDAVP stimulation test

IMAGING

□ CT □ MRI □ others

Findings:

□ unilateral adrenal adenoma □ bilateral adrenal adenoma

□ pituitary adenoma □ others……..

- Size of adenoma (largest diameter in cm)…….

Treatment

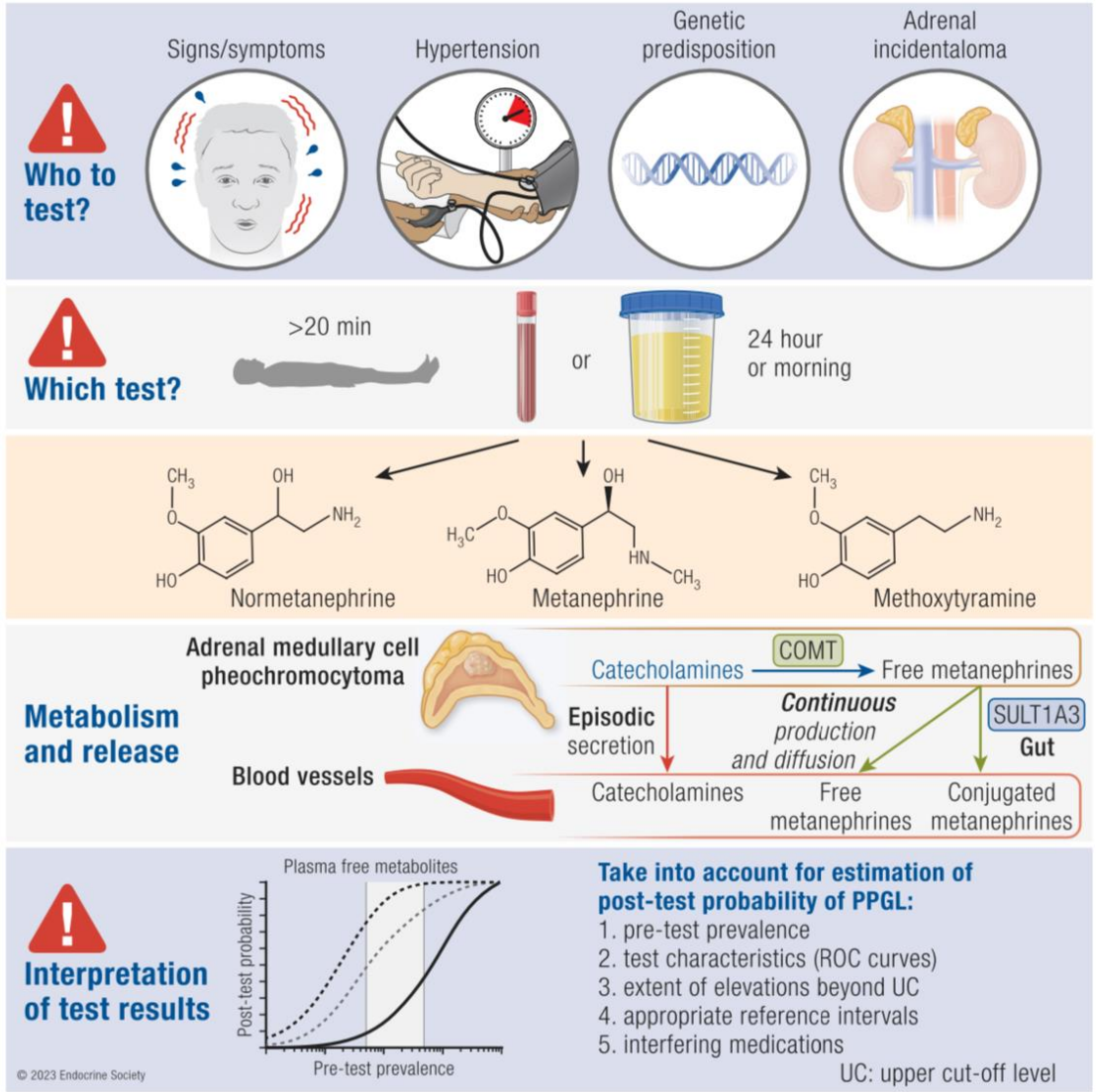
- Supportive
  - Metabolic complications: DM, hypertension, dyslipidemia
  - Infection, thromboembolism, osteoporosis if present

- Specific treatment
  - Unilateral cortisol-producing adrenal adenoma
    - Laparoscopic adrenalectomy → postoperative adrenal insufficiency
      → ***Glucocorticoid replacement (until HPA axis recovery) & advise sick day management***

  - Adrenocortical carcinoma
    - Adrenalectomy ± adjuvant treatment if indicated
  - Cushing's disease (Pituitary Cushing's)
    - Transsphenoidal surgery with tumor removal
    - Remission – postoperative cortisol = 2 mcg/dL

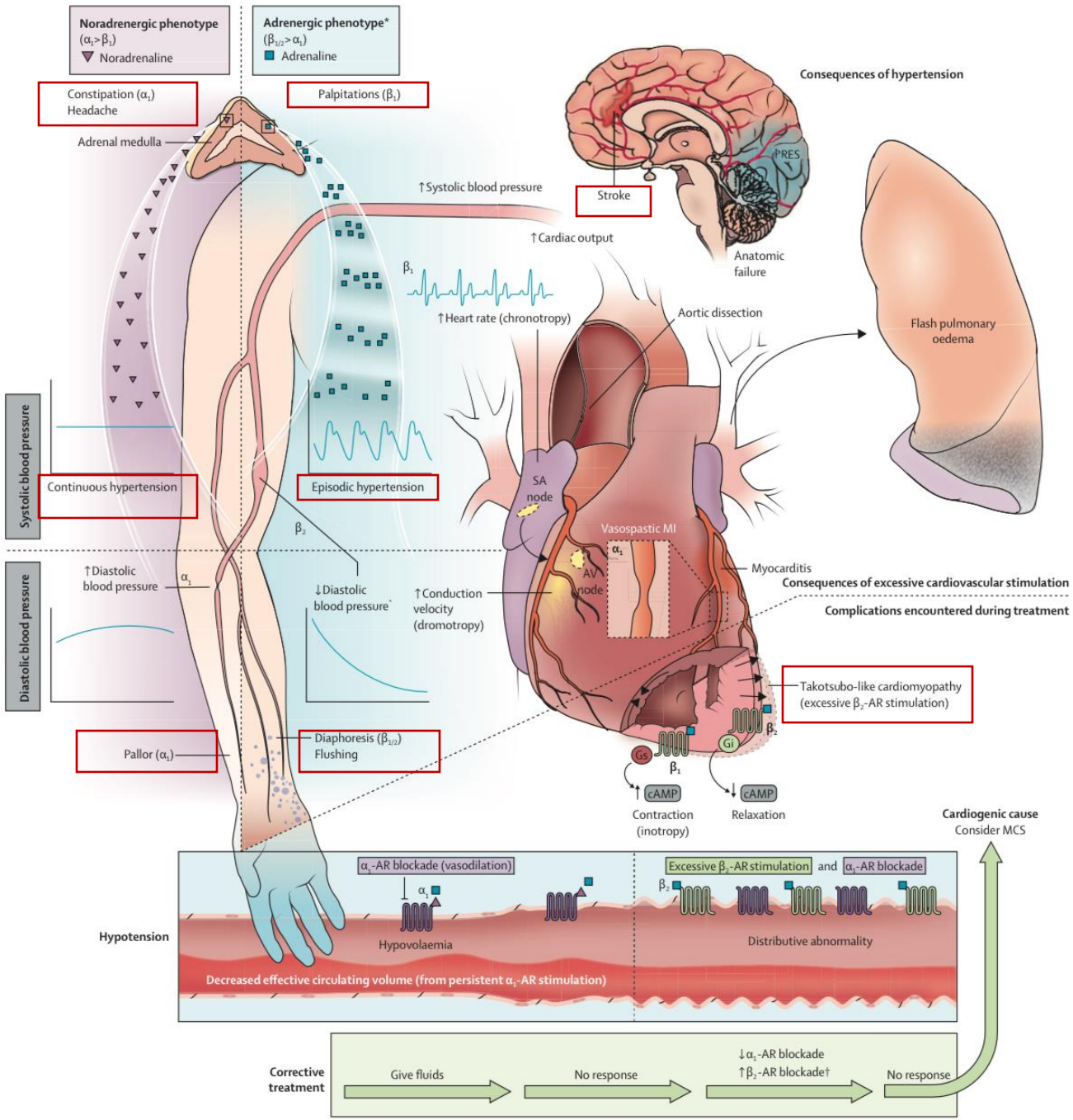
Image from Fleseriu M et al. Lancet Diabetes Endocrinol 2021. PMID: 34687601.

Pheochromocytoma

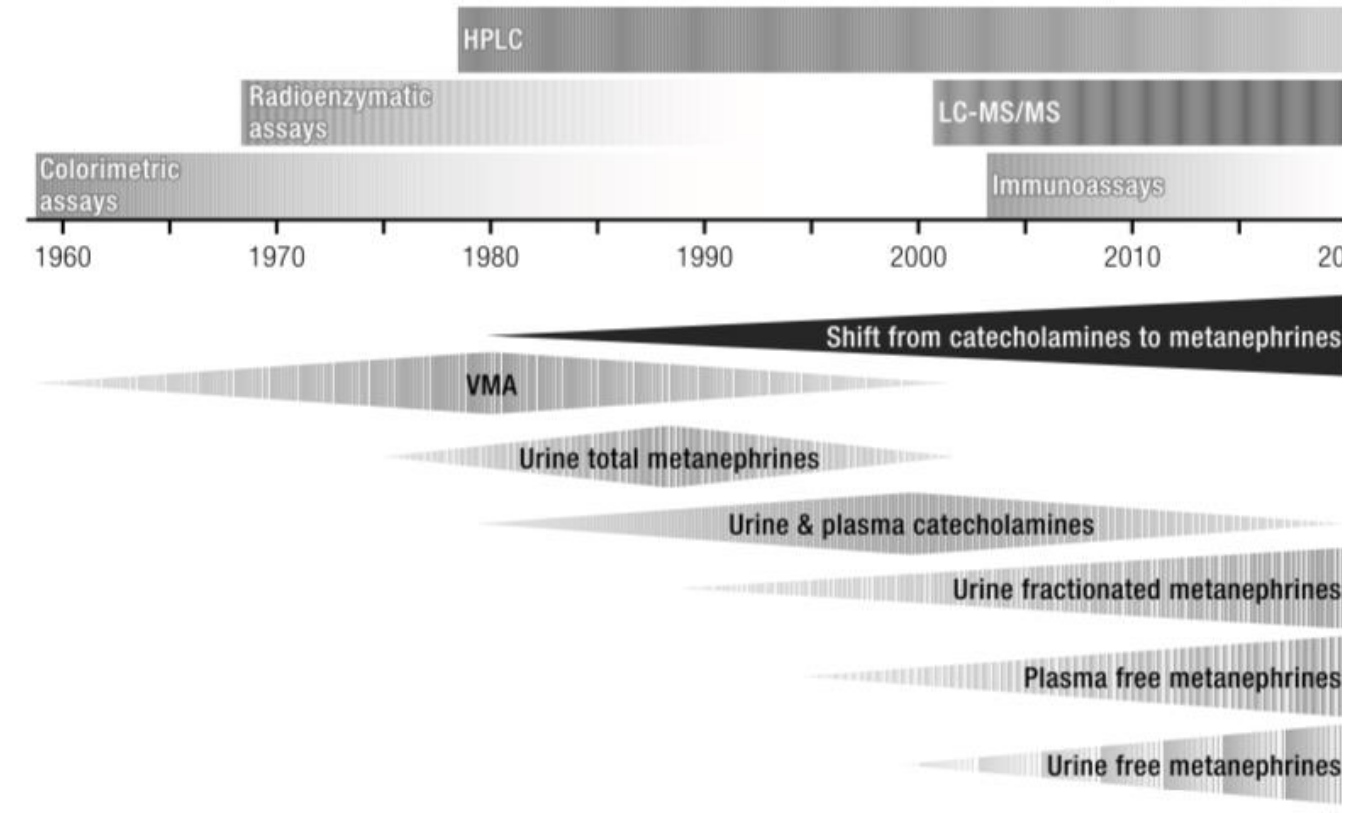


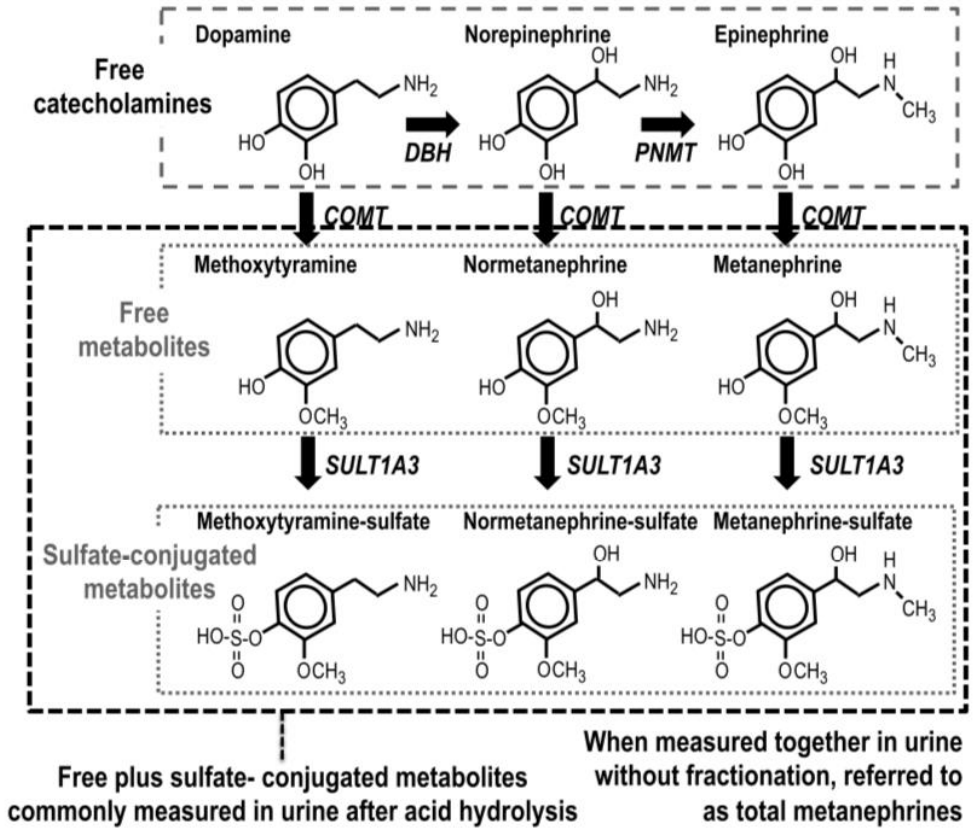
Eisenhofer G et al. Endocr Rev 2023. PMID: 36996131.

Signs and Symptoms of Catecholamine Excess



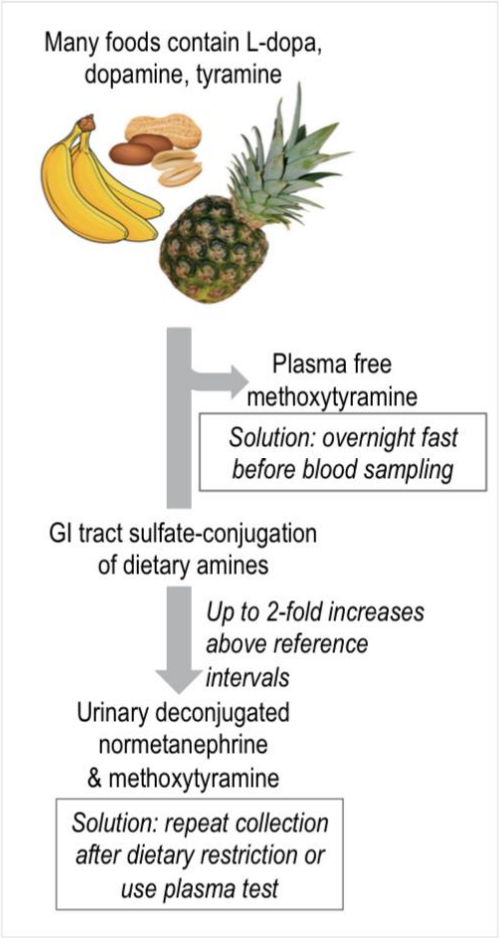
Biochemical Testing





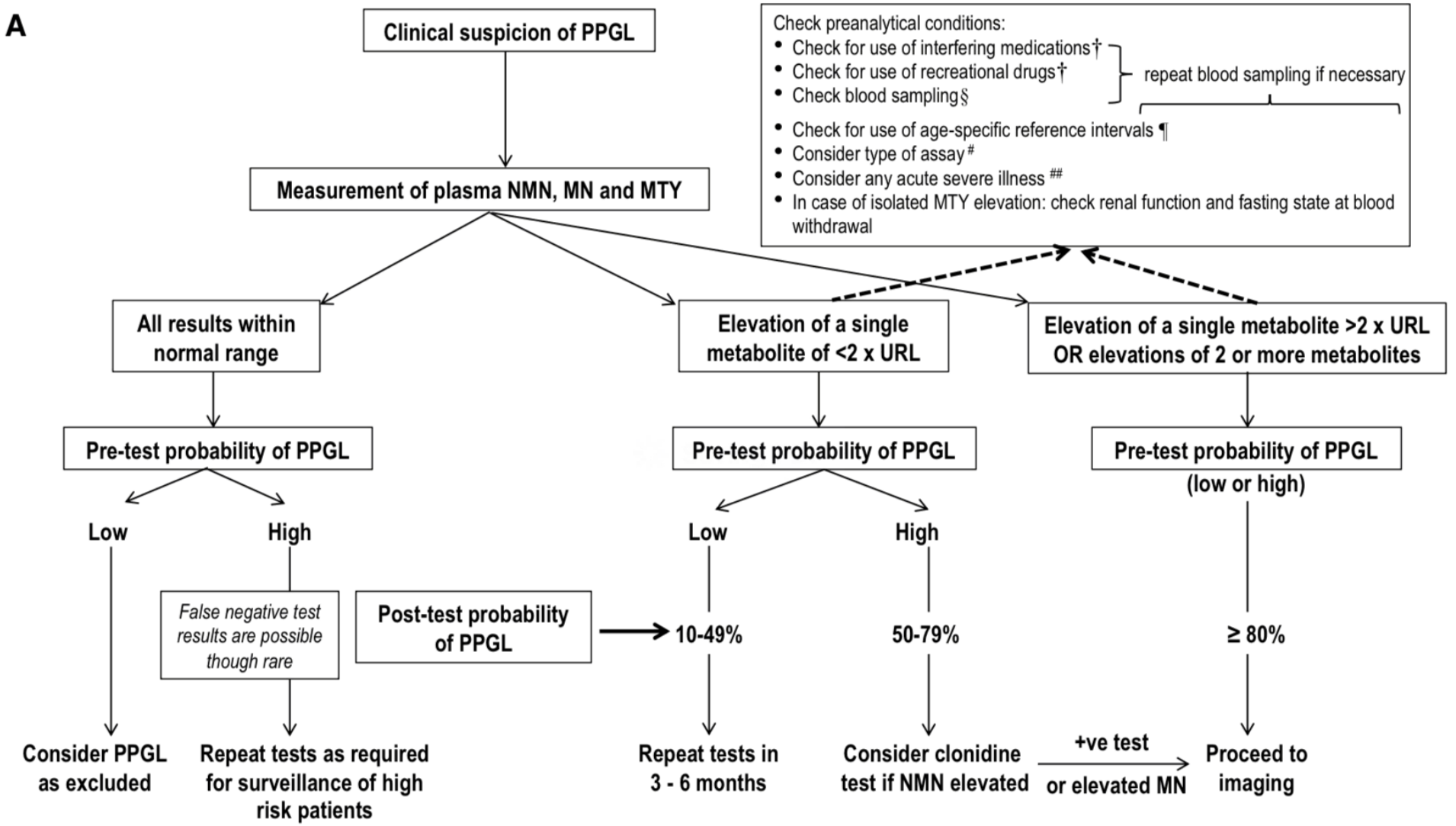
Eisenhofer G et al. Endocr Rev 2023. PMID: 36996131.

Foods and certain drugs can interfere with biochemical testing.



Drug category	Pharmacodynamic actions	Main impact
Stimulants		
Nicotine	• Activation of nicotinic cholinergic receptors	Increased adrenal epinephrine secretion
Caffeine	• Mobilization of intracellular calcium stores	Increased adrenal epinephrine secretion
Sympathomimetics		
Amphetamine Methamphetamine	• Increased release of monoamines from vesicular stores of sympathetic nerves • Inhibition of monoamine oxidase • Blockade of neuronal cell membrane norepinephrine (NE) transporters (NET)	Increased NE concentrations in the neuronal cytoplasm Reversed transport of NE by NET from cytoplasm to extracellular space Increased NE escape from reuptake
Ephedrine Pseudoephedrine	• Activation of alpha and beta-adrenergic receptors • Inhibits function of vesicular monoamine transporters • Inhibits NE reuptake (indirectly)	Increased NE release Increased NE release from secretory vesicles
Norepinephrine reuptake blockers		
Tricyclic antidepressants Venlafaxine/Duloxetine Cocaine	• Blockade of neuronal cell membrane NE transporters • Centrally mediated sympathoinhibition	Decreased sympathetic nerve firing and secretion of NE from sympathetic nerves, but opposing increased escape of NE from reuptake after neuronal secretion
Alpha$_2$ adrenoreceptor antagonists		
Phenoxybenzamine Mirtazapine Yohimbine	• Antagonism of alpha2-adrenoreceptors at central sympathoinhibitory sites and on sympathetic neurons	Increased sympathetic nerves firing secretion of NE from sympathetic nerves
Monoamine oxidase (MAO) inhibitors	• Blockade of the deamination of the O-methylated catecholamine metabolites	Increased plasma and urinary metanephrines with normal catecholamines
Atypical antipsychotics		
Quetiapine, Clozapine, Risperidone	• Inhibition of dopaminergic, adrenergic, and serotoninergic receptors • Antagonism to α_2-adrenoreceptors	Increased secretion of NE from sympathetic nerves

Eisenhofer G et al. Endocr Rev 2023. PMID: 36996131.

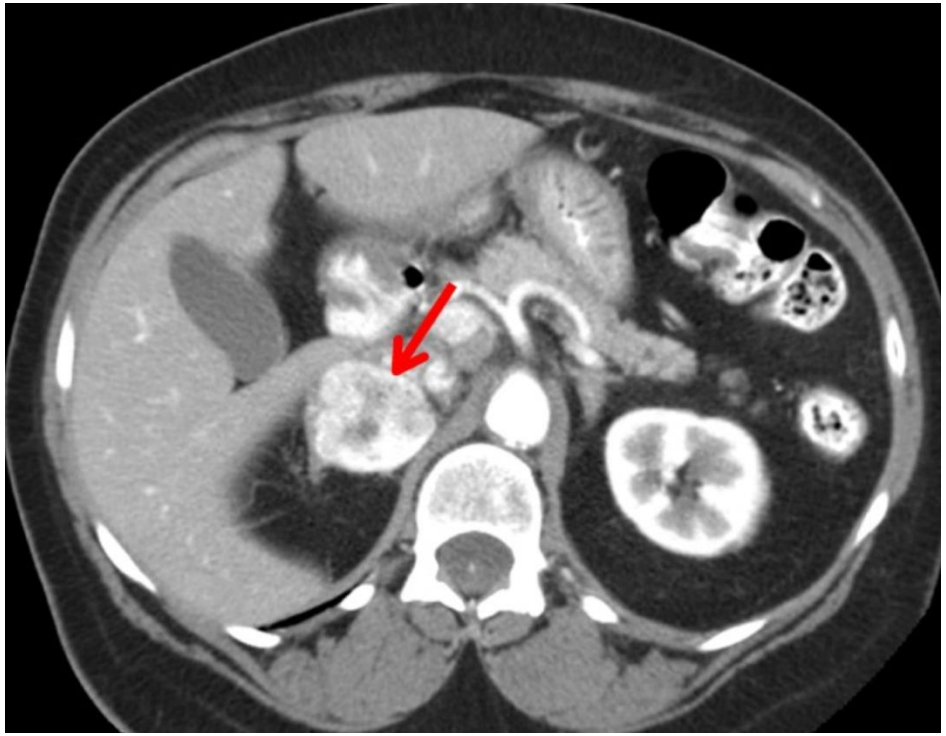


Urine: >3x URL

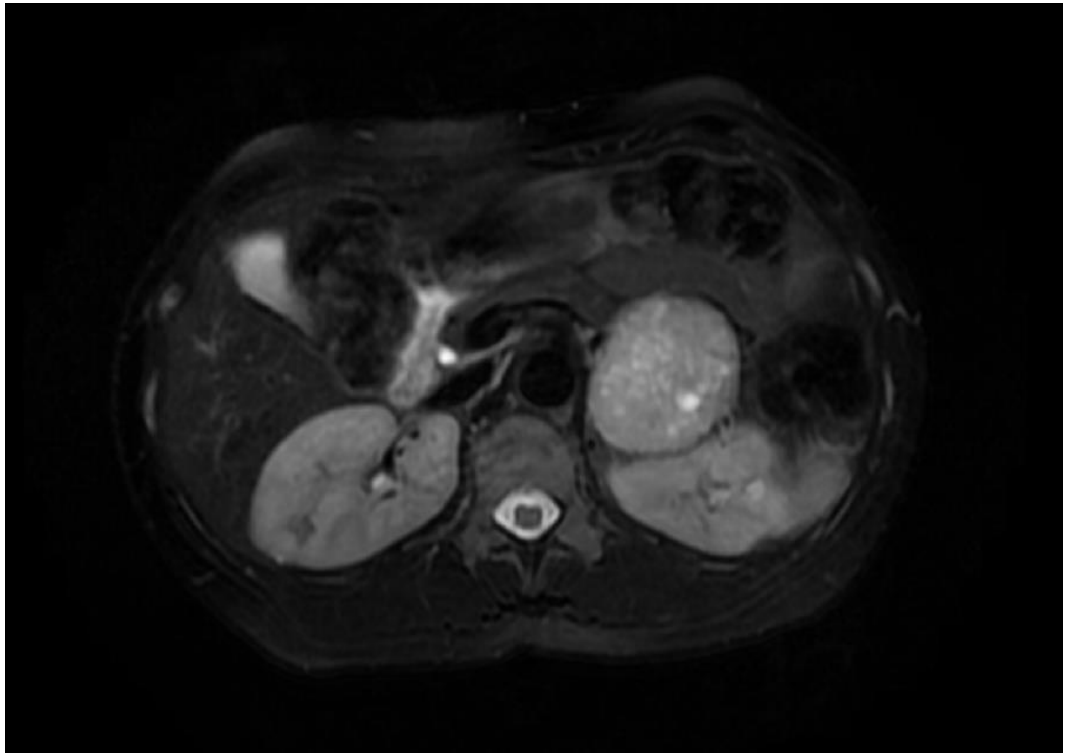
High probability of PPGL: tested because of previous PPGL, hereditary predisposition, adrenal incidentaloma
Low probability of PPGL: tested because of signs and symptoms of catecholamine excess

Eisenhofer G et al. Endocr Rev 2023. PMID: 36996131.

Pheochromocytoma: Imaging



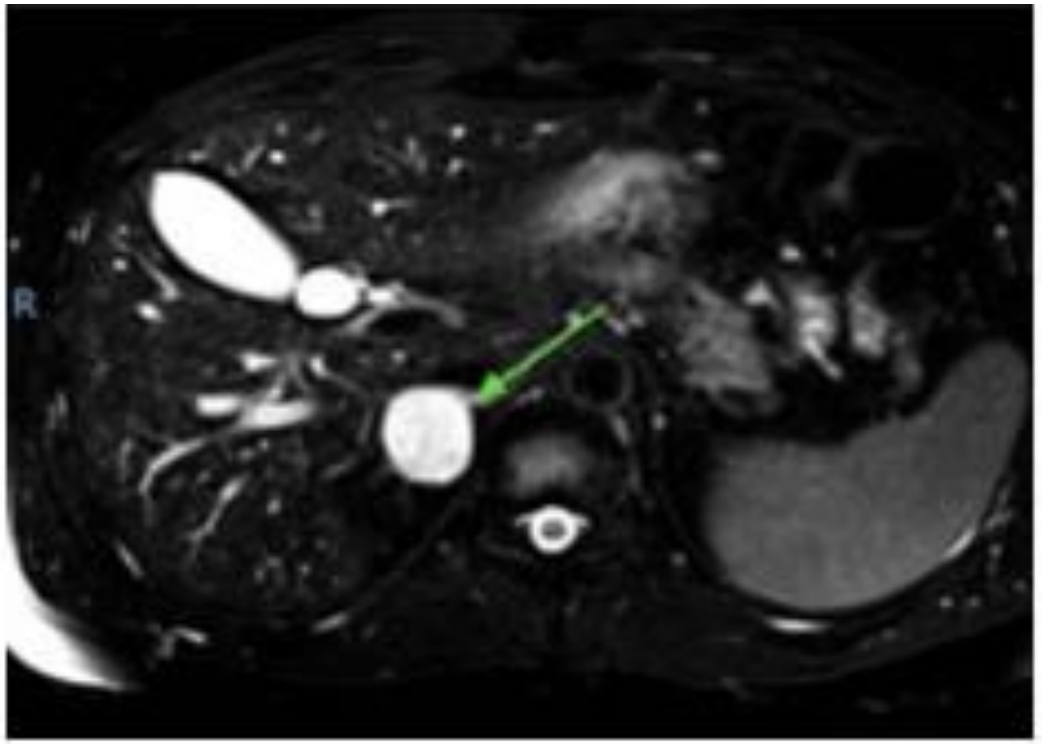
Lipid-poor, inhomogeneous enhancement



Hypersignal intensity in T2W

Do not biopsy !!!!!!!!!!

CUEZ endocrine



T2 weighted MR with fat suppression showing a hypersignal intensity lesion at right suprarenal area (arrow)

“Light bulb sign”

- Sign นี้พบได้ในภาพ MRI ของ pheochromocytoma
- โดยจะเห็นลักษณะ lesion เป็น hypersignal intensity ใน T2W คือดูแล้วให้ลักษณะสว่างจ้าออกมา (bright lesion) มี report ว่าพบ classic sign นี้ในประมาณ 11-65% ของผู้ป่วย pheochromocytoma เนื่องจากหลายๆ เหตุผล เช่น ตัวก้อนอาจจะมีส่วนที่เป็น cystic หรือ necrotic area ฯลฯ
- เอาเป็นว่า ถ้าเห็น sign นี้ อย่าเพิ่ง biopsy นะคะ เนื่องจากถ้าเป็น pheochromocytoma จริงๆ และ biopsy ไป จะทำให้เกิด pheochromocytoma crisis ได้ค่ะ

AJR 2013; 200:370–378; Abdom Radiol (2017) 42:2779

Perioperative Management

Drug	Starting dose	Incremental dose steps[a]	Dose range	Comments
phenoxybenzamine	10mg q.d.	20mg	10-140mg	Preferably started at least 7-14 days prior to surgery, also in case of normotension. Doses higher than starting dose are administered b.i.d.
or				
doxazosin ER	4mg q.d.	4mg	4-56mg	
nifedipine ER	30mg q.d.	30mg	30-90mg	Add-on to α-adrenergic receptor blockade in case of persistent hypertension (BP supine >130/80 mmHg, SBP upright >110 mmHg)
or				
amlodipine	5mg q.d.	5mg	5-10mg	
or				
metyrosine	250mg t.i.d.	250-500mg	750-2000mg	
metoprolol ER	50mg q.d.	50mg	50-200mg	Add-on in case of tachycardia (HR supine >80bpm, HR upright >100bpm). Preferably be started after sufficient preparation with α-adrenergic receptor blockade (≥3-4 days)
or				
propranolol	20mg t.i.d.	20mg	20-240mg	
or				
atenolol	25mg q.d.	25mg	25-100mg	
high sodium chloride diet	≥15 grams	-	-	Restoration of intravascular volume depletion; prevention of preoperative orthostatic hypotension and postoperative hypotension
and				Diet should be started >7-14 days before surgery
saline 0.9% i.v.	2L /24h	-	-	Intravenous saline should be started 24h before surgery

Supine BP >160/100 mmHg 24h before planned surgery; consider postponement of surgery. Surgery is usually performed in the morning, and the last dosage of each oral drug should preferably be administered on the evening before surgery. In case surgery begins after 12.00 AM, the last dosage of each oral drug should be administered at 07.00 AM on the day of surgery. Only the administration of 0.9% saline should be continued during surgery.
Abbreviations: ER, extended-release; q.d., one a day; b.i.d., twice daily; t.i.d., 3 times daily; i.v., intravenous; BP, blood pressure; SBP, systolic blood pressure; HR, heart rate.
[a]Dose adjustments preferably every 2–4 days at the discretion of the clinician and guided by the response on blood pressure and/or heart rate.

Preoperagive goal

Blood pressure

- Seated <130/80 mmHg and
- Upright SBP >90 mmHg

Heart rate

- Seated 60-70/min
- Upright 70-80/min

Berends AMA et al. J Clin Endocrinol Metab 2020. PMID: 32726444.

Pheochromocytoma: Treatment

- Preoperative: Adequate alpha-blockers, Na intake
- Perioperative medical management
  - Admit 7-14 days prior to surgery
  - High Na intake and adequate fluid
  - Monitor BP and PR
- Surgery
  - Laparoscopic adrenalectomy
  - Consider open adrenalectomy for large (> 6cm) or invasive PHEOs
- Lifelong follow up
  - Clinical + metanephrines
- Always look for syndromic PPGL
  - Genetic counseling

PPGL, pheochromocytomas/paraganglioma

Syndromic PPGL

Syndrome	Clinical findings
Multiple endocrine neoplasia type 2A	***Medullary thyroid cancer***, primary hyperparathyroidism, and cutaneous lichen amyloidosis
Multiple endocrine neoplasia type 2B	***Medullary thyroid cancer***, mucocutaneous neuromas, skeletal deformities, joint laxity, myelinated corneal nerves, and intestinal ganglioneuromas
Von Hippel-Lindau syndrome Normetaneprine เด่น	Hemangioblastoma, retinal angioma, clear cell RCC, pancreatic NET, and serous cystadenomas, endolymphatic sac tumors of the middle ear, papillary cystadenomas of the epididymis and broad ligament
Neurofibromatosis type 1	Neurofibromas, multiple café-au-lait spots, axillary and inguinal freckling, iris hamartomas (Lisch nodules), bony abnormalities, CNS gliomas, macrocephaly, cognitive deficits

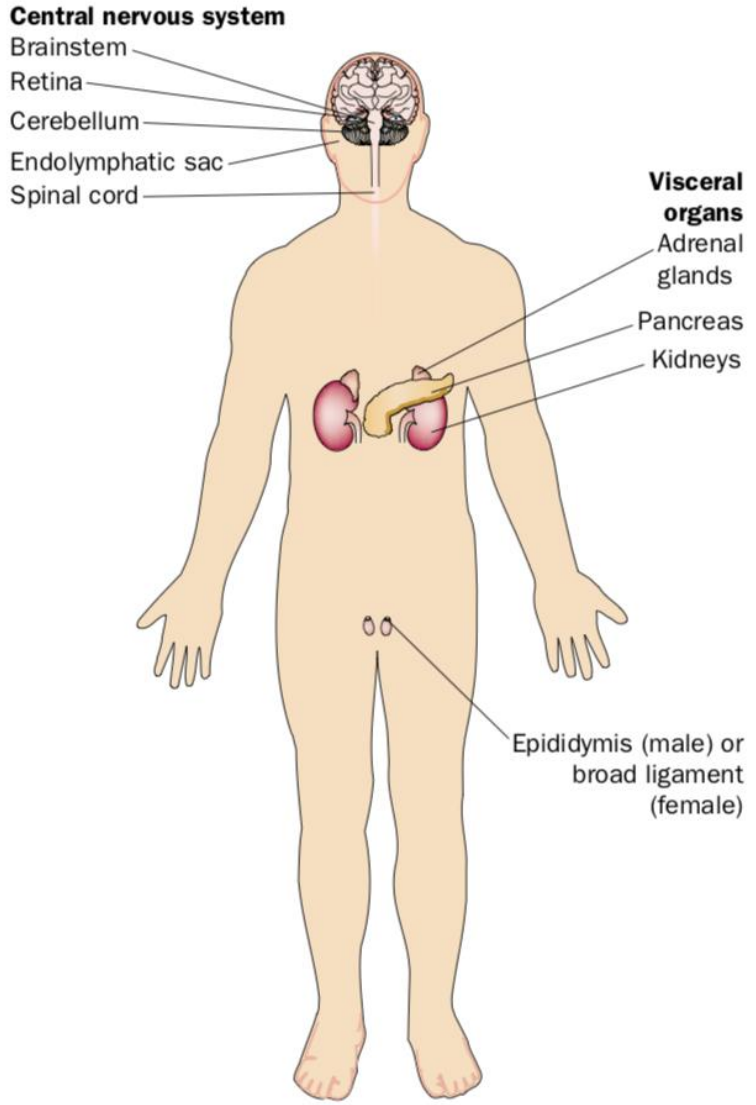
J Clin Endocrinol Metab, June 2014, 99(6):1915–1942

Von Hippel-Lindau Syndrome (VHL)

	Mean (range) age of onset (years)	Frequency in patients (%)
CNS		
Retinal haemangioblastomas	25 (1–67)	25–60%
Endolymphatic sac tumours	22 (12–50)	10%
Craniospinal haemangioblastomas		
Cerebellum	33 (9–78)	44–72%
Brainstem	32 (12–46)	10–25%
Spinal cord	33 (12–66)	13–50%
Lumbosacral nerve roots	Unknown (..)	<1%
Supratentorial	Unknown (..)	<1%
Visceral		
Renal cell carcinoma or cysts	39 (16–67)	25–60%
Phaeochromocytomas	30 (5–58)	10–20%
Pancreatic tumour or cyst	36 (5–70)	35–70%
Epididymal cystadenoma	Unknown (..)	25–60%
Broad ligament cystadenoma	Unknown (16–46)	Unknown

See references 5,7–17.

Table 1: **Frequency of lesions and age at onset of von Hippel-Lindau disease lesions**



Lonser RR et al. Lancet 2003. PMID: 12814730.

Thyroid Function Test

Conditions	FT3, FT4	TSH
Primary hyperthyroidism	↑	↓
Subclinical hyperthyroidism	↔	↓
Hypothyroidism (primary or secondary)	↓	↑
Subclinical hypothyroidism Non-thyroidal illness (recovery phase)	↔	↑
TSH-secreting pituitary adenoma Resistance to thyroid hormones Drugs, assay interference	↑	↑/↔
Secondary hypothyroid Non-thyroidal illness	↓	↓/↔

Adapted from Best Practice & Research Clinical Endocrinology & Metabolism 27 (2013) 745–762

Etiology of Thyrotoxicosis

TSH producing pituitary adenoma
(central hyperthyroidism)

Pregnancy
Trophoblastic tumor

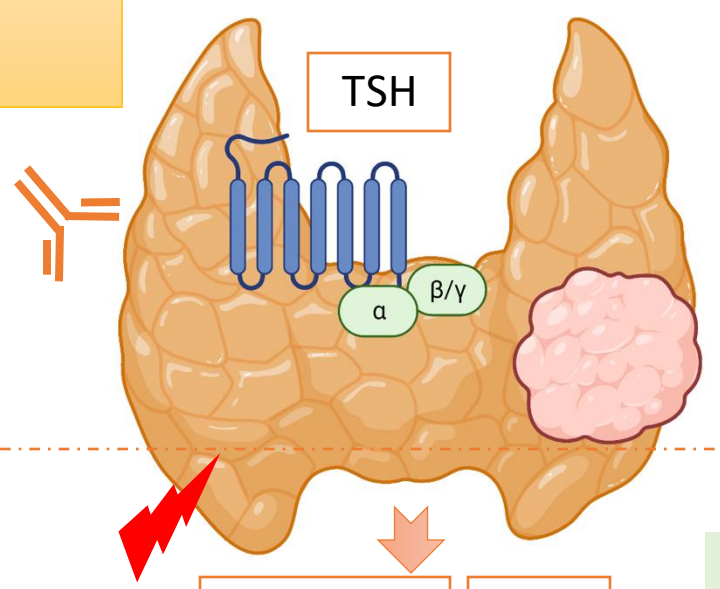
Other causes
- Amiodarone
- Immune check point inhibitors
- COVID-19 related (infection/vaccination)

hCG

Graves' disease

TSH

TSH receptor antibody (TRAb)



Nodular thyroid disease
- Toxic adenoma
- Toxic nodular goiter

"Hyperthyroid" → High RAIU

Low RAIU

FT4 FT3

Thyroiditis

Ectopic thyroid hormone production
- Struma ovarii
- Functioning metastasis follicular carcinoma

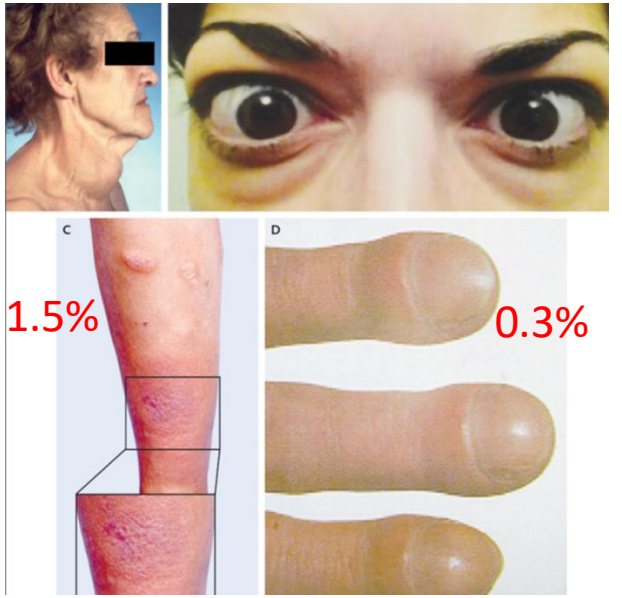
Exogenous thyroid hormone
(Thyrotoxicosis factitia)

Credit slides: อ. ปนัดดา

RAI: radioiodine uptake

Etiology	Treatment
Graves' disease	Antithyroid drug (12-18 mo) RAI Thyroidectomy
Nodular thyroid disease	Antithyroid drug long-life RAI Thyroidectomy
Thyroiditis	Beta-blockers NSAIDs, prednisolone
TSH producing pituitary adenoma	Transsphenoidal pituitary surgery
Ectopic thyroid hormone production	Tumor removal
hCG related hyperthyroidism	Supportive treatment Suction & Curettage
Thyrotoxicosis factitia	Off medication

Graves' disease



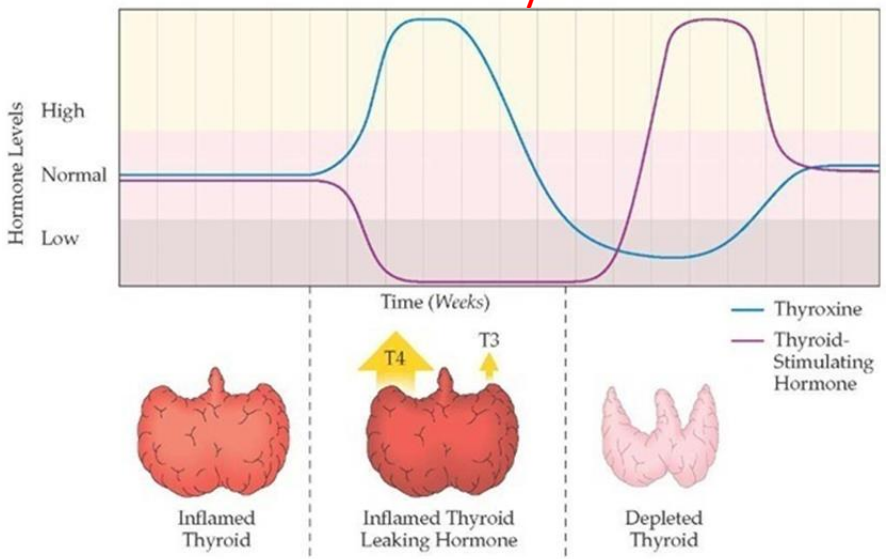
25%

1.5%

0.3%

Thyroiditis

Transient thyrotoxicosis



Credit slides: อ. ปนัดดา

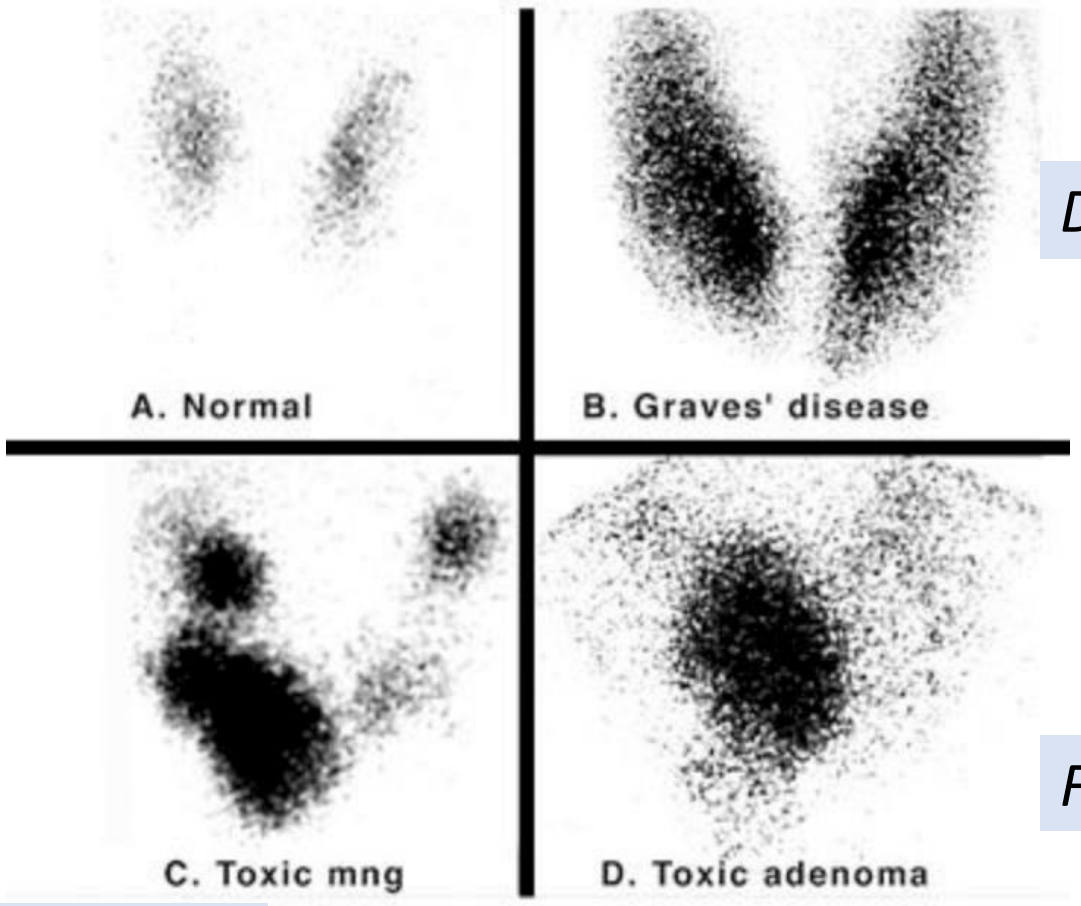
Etiology	TRAb	Thyroid uptake	Thyroid ultrasound and color flow Doppler
Graves' disease	High	High	Diffuse increase Doppler flow
Nodular thyroid disease Thyroid scan	Low	High	Nodular thyroid Increase Doppler flow at nodule
Thyroiditis High ESR	Low	Low	Decrease Doppler flow
TSH producing pituitary adenoma MRI pituitary	Low	High	Diffuse increase Doppler flow
Ectopic thyroid hormone production Pelvic ultrasound, total body scan	Low	Low at thyroid Uptake outside thyroid	Decrease Doppler flow
hCG related hyperthyroidism High hCG level	Low	High	
Thyrotoxicosis factitia Absent of goiter, low thyroglobulin level	Low	Low	

sensitivity 96–97% and specificity 99%

	TRAb	TPOAb	TGAb
Graves' disease	80-95%	50-80%	50-70%
Autoimmune thyroid disease	10-20%	90-100%	80-90%

Credit slides: อ. ปนัดดา

Radioactive Iodine Uptake (neck)



Diffuse increased uptake

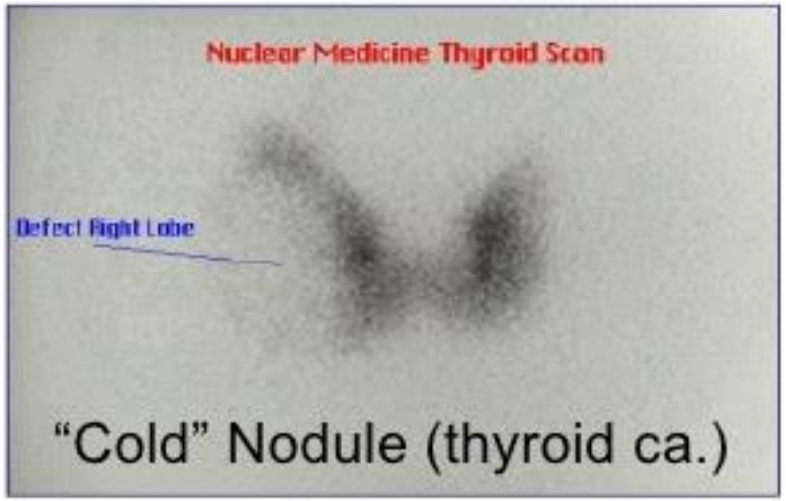
Focal uptake in the adenoma

Multiple areas of focal increased & suppressed uptake

Thyroid Scan

- To determine the etiology of hyperthyroidism in the presence of thyroid nodularity.

"Hot" Nodule



"Cold" Nodule (thyroid ca.)

Images from https://www.slideshare.net/roger961/thyroid-physiology-and-disorders

Treatment: Graves' Disease

Rx	Patient	Pros	Cons
ATDs	• Young (age < 40 yr), short duration, mild symptom, small goiter • Contraindication to thyroidectomy or RAI	• Convenient • Avoidance of lifelong thyroid hormone replacement, surgical risk and radioactivity exposure	• Long duration of treatment, need monitoring • Risk of relapse after stop ATDs (50%) • Risk of side effect form ATDs • Teratogenic effect esp. MMI in 1st trimester
RAI	• Moderate to severe symptom • Age > 40 yr • Relapse after ATDs • Allergy to ATDs	• Definite treatment • Avoidance of surgical risk and side effect form ATDs	• Time to Euthyroidism (6 weeks to > 3 months) • Permanent hypothyroid (50%) • Worsening Graves' ophthalmopathy (GO) (20%) • Avoid pregnancy within 6 months after treatment • **Contraindication: pregnancy, breast feeding, severe Graves' ophthalmopathy**
Thyroidectomy	• Moderate to severe symptom, large goiter • Moderate to severe GO • Other conditions that need surgery: thyroid carcinoma, hyperparathyroidism	• Definite and rapid resolution • Avoidance side effect form ATDs and radioactivity exposure	• Permanent hypothyroid • Surgical and anesthetic complications • Expensive

Credit slides: อ. ปนัดดา

Hypothyroidism: Etiology

Primary

- Autoimmune
- Postablative or surgery
- Drugs
- Iodine deficiency
- Infiltrative disorders
- Congenital hypothyroidism
- Overexpression of D3 (infantile hemangioma)

Secondary

- Hypopituitarism
- Isolated TSH deficiency (rare)

Hypothyroidism: Screening

- Autoimmune disease, anti-TPO positive
- ***T1DM, Turner's syndrome, Down's syndrome***
- History of neck surgery, radiation
- Drugs: Interferon (IFN), Tyrosine kinase inhibitor (TKI), amiodarone
- Unexplained depression, cognitive dysfunction
- Pregnancy with recurrent abortion

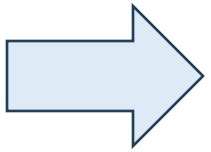
Hypothyroid: Treatment

- Type: L-T4
- Dose: 1.6 mcg/kg/day
  - *can be lower in patients with CV compromise/elderly*
- Monitor
  - Clinical + labs
  - Primary hypothyroidism: TSH in reference range
  - Secondary hypothyroidism: FT4 (upper half of normal limits)

Thyroid Nodules: Diagnostic Tools

- Serum TSH
- Ultrasound thyroid
  - Size, shape, margin, echogenicity content, microcalcification, vascularity
  - Cervical lymph node

Risk stratification



Fine needle aspiration (FNA)

Thyroid cytology

Bethesda system

- Other imaging modality
  - Elastography
  - Artificial intelligence/ Computer aided diagnosis
  - Radiomics
  - Nuclear medicine
  - 18-FDGs-PET

Credit slides: อ. ปนัดดา

Ultrasound Risk Classification of Thyroid nodule

System	Summary	Categories	POM	Biopsy threshold
ATA	Pattern recognition based on ultrasound features (composition, echogenicity, margin, shape, echogenic foci, lymphadenopathy)	Benign	0	No biopsy
		Very low risk	<3%	≥2 cm or no biopsy
		Low risk	5-10%	1.5
		Intermediate risk	10-20%	≥1 cm
		High risk	70-90%	≥1 cm
ACR-TIRADS	Weighted point based system (composition, echogenicity, shape, margin, echogenic foci)	Benign (TIRADS 1)	<2%	No biopsy
		Not suspicious (TIRADS 2)	<2%	No biopsy
		Mildly suspicious (TIRADS 3)	5%	FNA≥2.5 cm
		Moderately suspicious (TIRADS 4)	5-20%	FNA≥1.5 cm
		Highly suspicious (TIRADS 5)	>20	FNA≥1 cm
K-TIRADS	Ultrasound patterns based on composition, echogenicity, and presence of suspicious ultrasound features	No nodule (1)	-	-
		Benign (2)	<3%	≥2 cm
		Low suspicion (3)	3-15%	≥1.5 cm
		Intermediate suspicion (4)	15-50%	≥1.0 cm
		High suspicion (5)	>60%	≥1.0 cm (>0.5 cm, selective)
EU-TIRADS	Ultrasound patterns according to composition, echogenicity, and risk features	EU-TIRADS 1—normal	0	-
		EU-TIRADS 2—benign	0	No FNA
		EU-TIRADS 3—low risk	2-4%	>2 cm
		EU-TIRADS 4—intermediate risk	6-17%	>1.5 cm
		EU-TIRADS 5—high risk	26-87%	>1 cm
AACE/ACE/AME	Ultrasound patterns according to composition, echogenicity, and risk features	Low risk	1%	>2 cm, increase in size, clinical risk features
		Intermediate risk	5-15%	>2 cm
		High risk	50-90%	≥1 cm
BTA	Categories based on presence of different ultrasound features (composition, vascularity, echogenicity, shape, calcifications, lymph nodes, margins)	U1—normal	-	Do not need biopsy, unless patient has statistically high risk of malignancy
		U2—benign		
		U3—indeterminate/equivocal	-	Thyroid biopsy recommended
		U4—suspicious		
		U4—malignant		

- Highest accuracy
- Largest reduction of biopsy number
- Lowest false negative rate

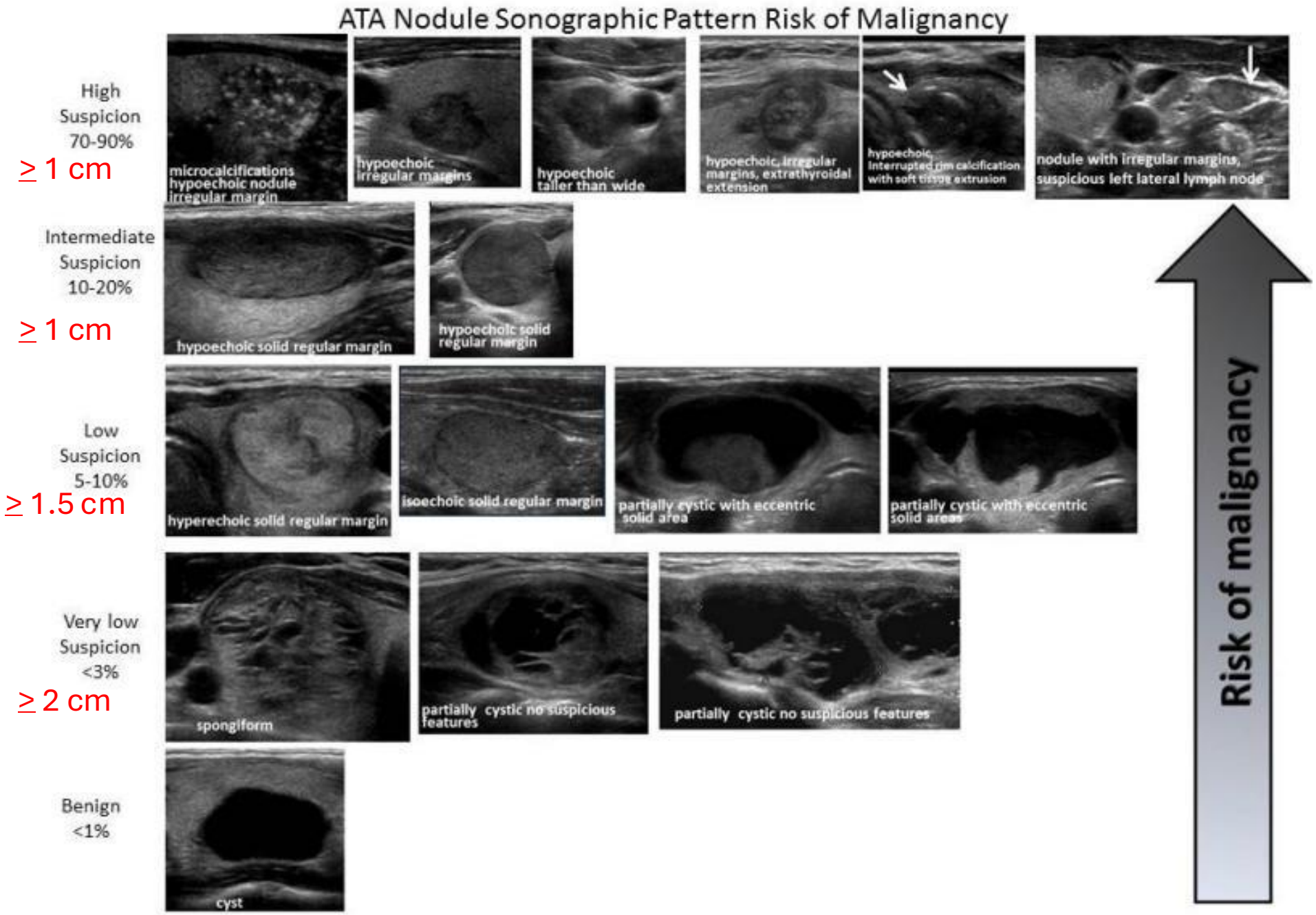
Limitation

- Inter-observer discrepancies
- Insufficient sensitivity for the diagnosis of follicular cancers and follicular variant of papillary cancers

- FNA is not recommended for all nodules < 1 cm
- Modify cut off by patients' risk factors and presence of lymph node

Credit slides: อ. ปนัดดา

BMJ 2020;368:l6670



ican Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

Credit slides: อ. ปนัดดา

ACR TI-RADS

https://tiradscalculator.com/

COMPOSITION (Choose 1)	
Cystic or almost completely cystic	0 points
Spongiform	0 points
Mixed cystic and solid	1 point
Solid or almost completely solid	2 points

ECHOGENICITY (Choose 1)	
Anechoic	0 points
Hyperechoic or isoechoic	1 point
Hypoechoic	2 points
Very hypoechoic	3 points

SHAPE (Choose 1)	
Wider-than-tall	0 points
Taller-than-wide	3 points

MARGIN (Choose 1)	
Smooth	0 points
Ill-defined	0 points
Lobulated or irregular	2 points
Extra-thyroidal extension	3 points

ECHOGENIC FOCI (Choose All That Apply)	
None or large comet-tail artifacts	0 points
Macrocalcifications	1 point
Peripheral (rim) calcifications	2 points
Punctate echogenic foci	3 points

Add Points From All Categories to Determine TI-RADS Level

0 Points	2 Points	3 Points	4 to 6 Points	7 Points or More
TR1 Benign — No FNA	**TR2** Not Suspicious — No FNA	**TR3** Mildly Suspicious — FNA if ≥ 2.5 cm; Follow if ≥ 1.5 cm	**TR4** Moderately Suspicious — FNA if ≥ 1.5 cm; Follow if ≥ 1 cm	**TR5** Highly Suspicious — FNA if ≥ 1 cm; Follow if ≥ 0.5 cm*

COMPOSITION	ECHOGENICITY	SHAPE	MARGIN	ECHOGENIC FOCI
Spongiform: Composed predominantly (>50%) of small cystic spaces. Do not add further points for other categories. *Mixed cystic and solid:* Assign points for predominant solid component. Assign 2 points if composition cannot be determined because of calcification.	*Anechoic:* Applies to cystic or almost completely cystic nodules. *Hyperechoic/isoechoic/hypoechoic:* Compared to adjacent parenchyma. *Very hypoechoic:* More hypoechoic than strap muscles. Assign 1 point if echogenicity cannot be determined.	*Taller-than-wide:* Should be assessed on a transverse image with measurements parallel to sound beam for height and perpendicular to sound beam for width. This can usually be assessed by visual inspection.	*Lobulated:* Protrusions into adjacent tissue. *Irregular:* Jagged, spiculated, or sharp angles. *Extrathyroidal extension:* Obvious invasion = malignancy. Assign 0 points if margin cannot be determined.	*Large comet-tail artifacts:* V-shaped, >1 mm, in cystic components. *Macrocalcifications:* Cause acoustic shadowing. *Peripheral:* Complete or incomplete along margin. *Punctate echogenic foci:* May have small comet-tail artifacts.

mm TR5 nodules.

Credit slides: อ. ปนัดดา

J Am Coll Radiol. 2017 May;14(5):587-595.

ACR-TIRADS Thyroid Nodule Sonographic Characterization and Scoring

Point	Composition	Echogenicity	Shape	Margin	Echogenic foci
0	Cystic Spongiform	Anechoic	Wider than tall	Smooth ill-defined	None Comet tails
1	Mixed cystic solid	Hyper/isoechoic			Macrocalcifications
2	Mostly solid or completely solid	Hypoechoic		Lobulated/irregular	Peripheral/rim
3		Very hypoechoic	Taller than wide	Extrathyroidal extension	Microcalcification

Individual Sonographic Features and Associated Points ACR TIRADs classification

Point	Description	Malignancy risk (%)	FNA threshold	Surveillance	Repeat ultrasound
0	**TR1**: benign	<2	No FNA	None	None
2	**TR2**: not suspicious	<2	No FNA	None	None
3	**TR3**: mildly suspicious	5	FNA ≥ 2.5 cm	Follow if ≥ 1.5 cm	1,3 and 5 y
4-6	**TR4**: moderately suspicious	5-20	FNA ≥ 1.5 cm	Follow if ≥ 1 cm	1,2,3 and 5 y
≥ 7	**TR5**: highly suspicious	≥ 20	FNA ≥ 1 cm	Follow if ≥ 0.5 cm	Annually for 5 y

Credit slides: อ. ปนัดดา

The 2023 Bethesda System for Reporting Thyroid Cytopathology

Diagnostic category	ROM, Mean % (range)	Usual management
I: Nondiagnostic	13 (5–20)	Repeat FNA with ultrasound guidance
II: Benign	4 (2–7)	Clinical and ultrasound follow-up
III: Atypia of undetermined Significance (AUS)	22 (13–30)	Repeat FNA, molecular testing, diagnostic lobectomy, or surveillance
IV: Follicular neoplasm	30 (23–34)	Molecular testing, diagnostic lobectomy
V: Suspicious for malignancy	74 (67–83)	Molecular testing, lobectomy or near-total thyroidectomy
VI: Malignant	97 (97–100)	Lobectomy or near-total thyroidectomy

Cytological Indeterminate Thyroid Nodule (CITN)

Credit slides: อ. ปนัดดา

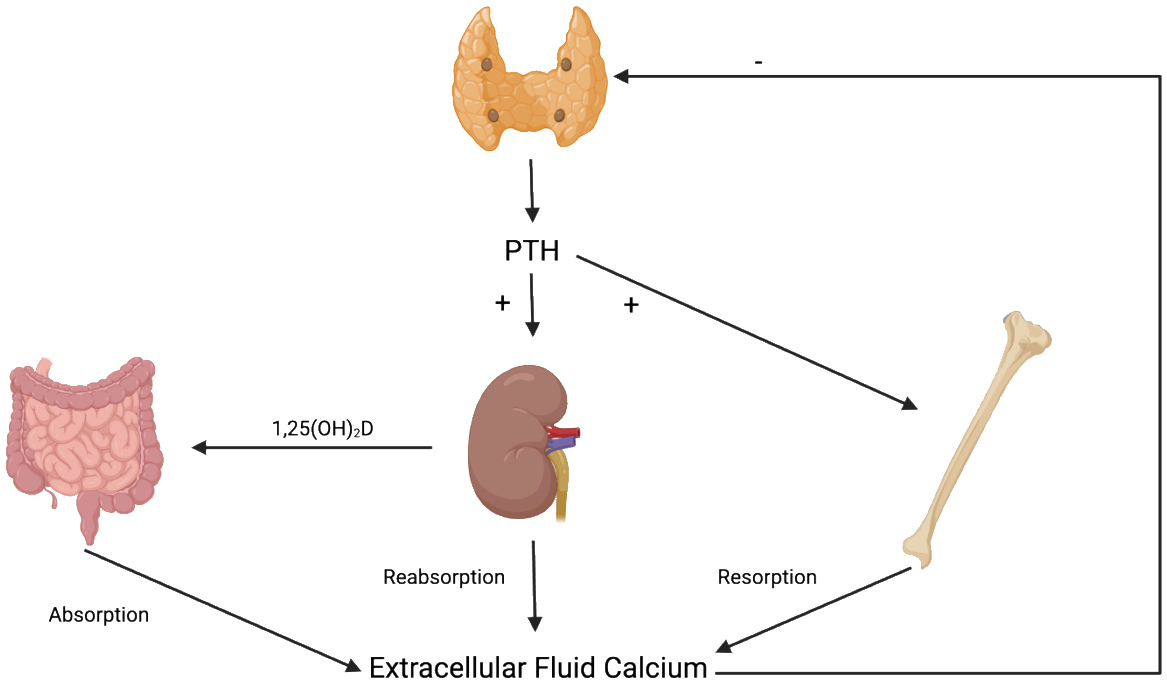
J Am Soc Cytopathol. 2023 Sep-Oct;12(5):319-325

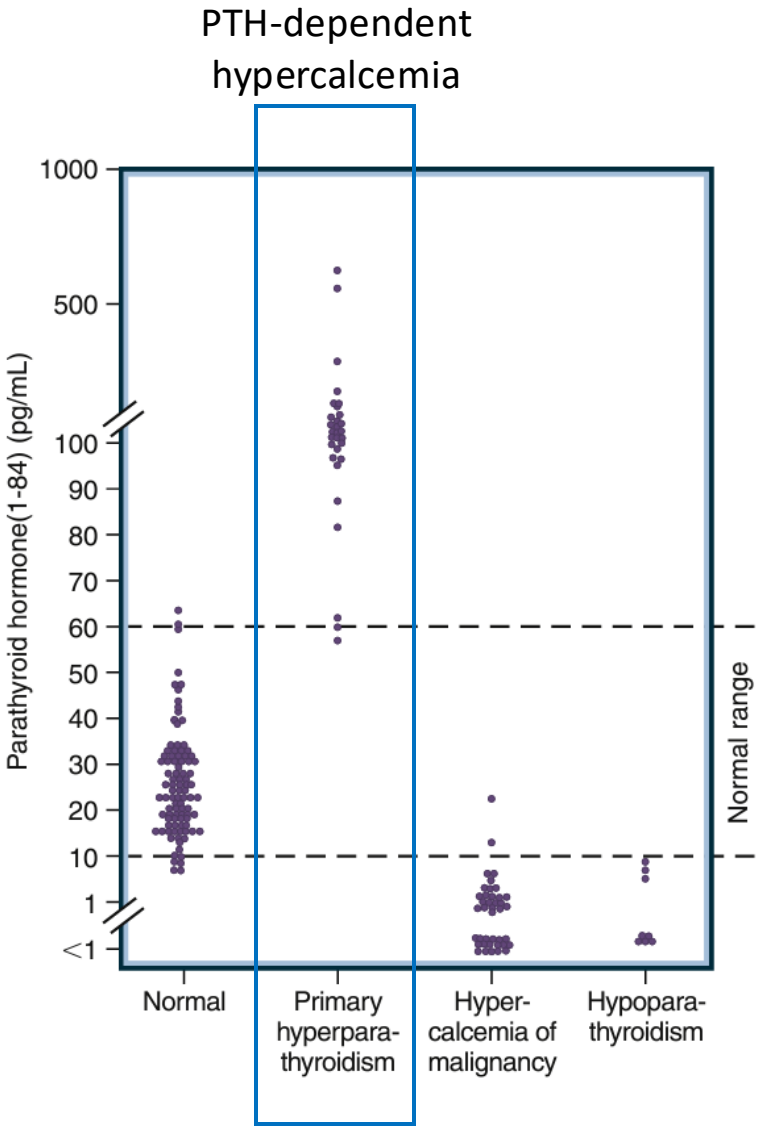
Calcium and Bone

Clinical Manifestation: Hypercalcemia

- **Renal**
  - Polyuria, nephrolithiasis, AKI and CKD
  - AVP resistance (nephrogenic DI)
  - Type 1 (distal) RTA
- **Gastrointestinal**
  - Constipation, anorexia, and nausea
- **Cardiac**
  - Shortened QT interval
- **Musculoskeletal**
  - Bone pain
- **Neuropsychiatric**
  - Anxiety, depression, cognitive dysfunction, lethargy, confusion, stupor, and coma

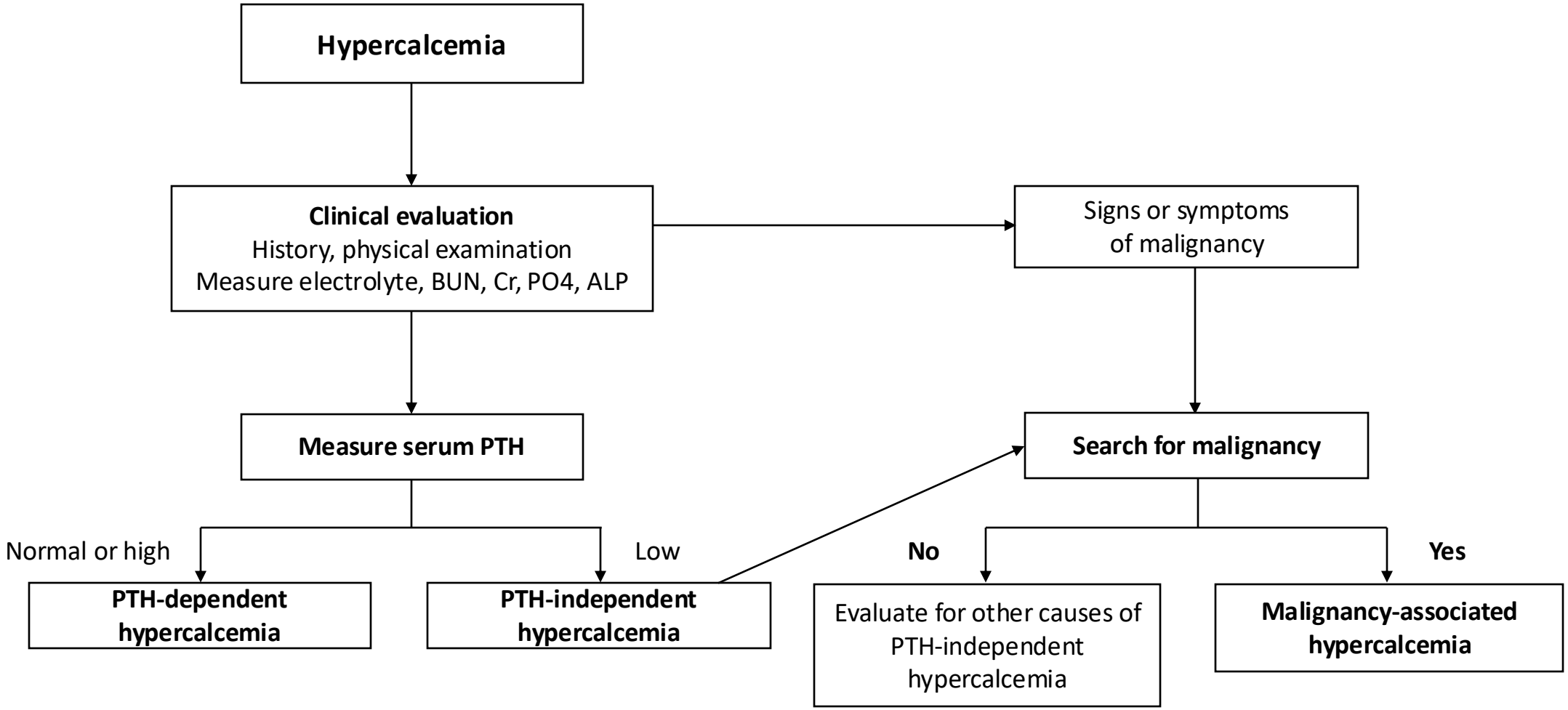
Calcium Homeostasis: PTH-calcium feedback loop





Adapted from Williams textbook of endocrinology 14th edition

Evaluation of Hypercalcemia



Adapted from Williams textbook of endocrinology 14th edition

Causes of Hypercalcemia

PTH-dependent hypercalcemia

- Primary hyperparathyroidism
- Tertiary hyperparathyroidism
- Familial hypocalciuric hypercalcemia
- Lithium-associated hypercalcemia
- Antagonistic autoantibodies to the calcium-sensing receptor

PTH-independent hypercalcemia

- Neoplasms
  - PTHrP dependent
  - Other humoral syndromes
  - Local osteolytic disease (including metastases)
- PTHrP excess (nonneoplastic)
- Excess vitamin D action
  - Ingestion of excess vitamin D or vitamin D analogues
  - Topical vitamin D analogues
  - Granulomatous disease
  - Williams syndrome
- Thyrotoxicosis
- Adrenal insufficiency
- Renal failure
  - Acute renal failure
  - Chronic renal failure with aplastic bone disease
- Immobilization
- Jansen disease
- Drugs
  - Vitamin A intoxication
  - Milk-alkali syndrome
  - Thiazide diuretics
  - Theophylline

PTHrP, Parathyroid hormone–related protein.

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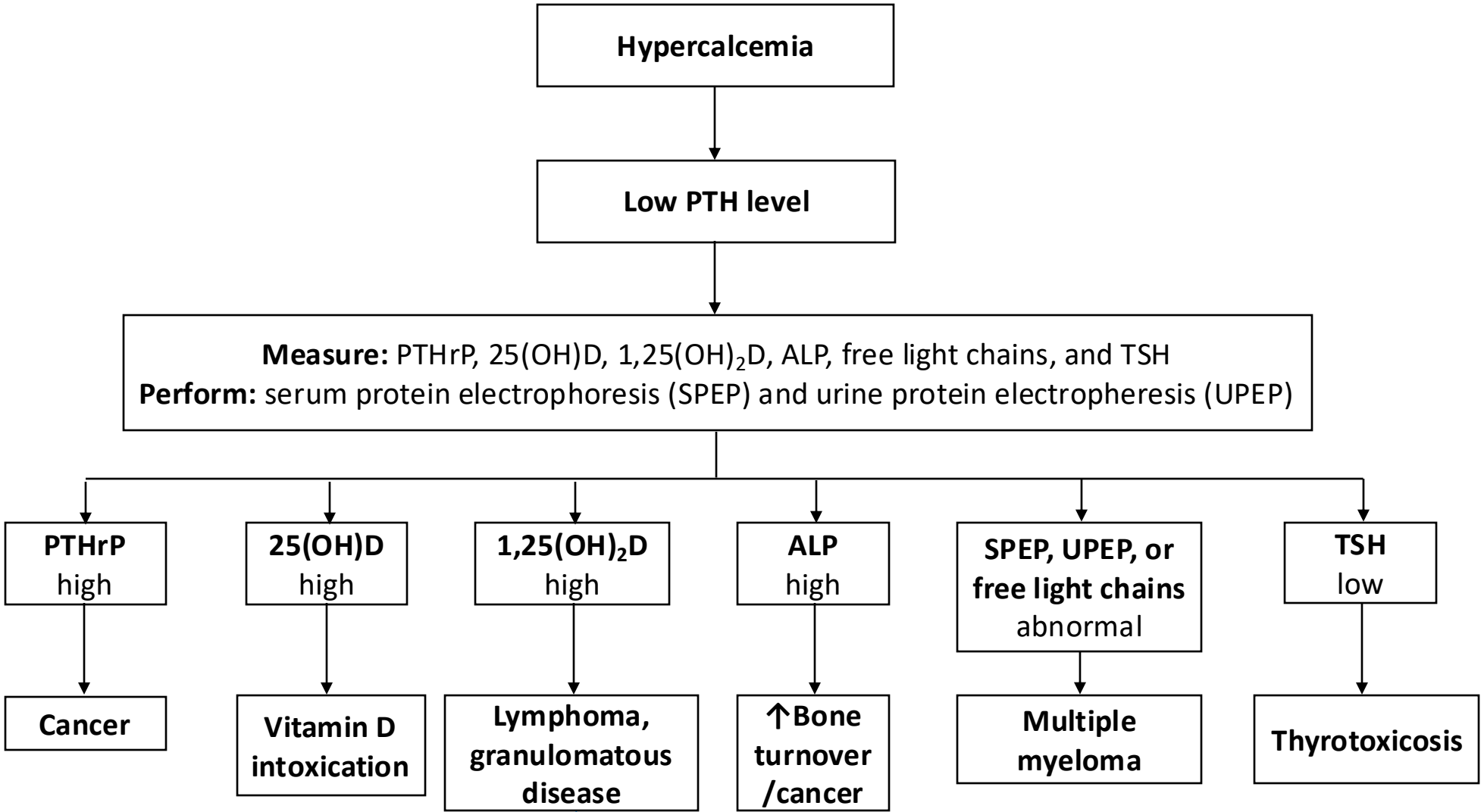
Evaluation of PTH-independent Hypercalcemia



Adapted from Crombie JL et al. Bad to the Bone. N Engl J Med. 2019 Jul 25;381(4):e9.

Hypercalcemia of Malignancy

- The mechanism of hypercalcemia can be multiple
  - Humoral hypercalcemia of malignancy
    - The most common tumors producing PTHrP include;
      - Squamous cell cancers (lung, head, neck, esophagus, cervix, vulva, and skin)
      - Breast cancer, renal cell cancer, bladder cancer
      - T-cell lymphoma associated with human T-cell lymphotropic virus type 1 (HTLV1)
    - High 1,25-dihydroxy vitamin D in Non-Hodgkin lymphoma

  - Local osteolytic hypercalcemia
    - This may result from tumors invading bone or stimulating bone resorption from the produced cytokines/chemokines.

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Clinical Practice Guideline

Treatment of Hypercalcemia of Malignancy in Adults: An Endocrine Society Clinical Practice Guideline

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El-Hajj Fuleihan G et al. J Clin Endocrinol Metab 2023. PMID: 36545746.

Treatment Regimen

Intervention/dose frequency	Mode of action	Onset of action	Median duration of action/ effect/proportion of subjects achieving normocalcemia	Adverse events/comments
Isotonic saline hydration/ Bolus of 1 to 2 L then 200 to 500 mL/hour to maintain urine output at 100 to 150 mL/hour.	Restores depleted intravascular volume. Enhances urinary calcium excretion.	Immediate	During infusion. Lowers calcium by 1 to 1.5 mg/dL (0.25 to 0.375 mmol/L) over first 24 hours.	Carefully assess for volume overload.
Loop diuretics*/ Furosemide 160 mg/d to 100 mg/h intravenously, or 40 to 60 mg/d orally only to be administered after volume repletion.	Increase urinary calcium excretion by inhibiting renal calcium reabsorption in the thick ascending loop of Henle, and proximal and distal renal tubules. Interferes with the chloride cotransport system.	Within 3 to 60 minutes	2 hours if bolus. During therapy if IV drip. Lowers calcium by 0.5 to 1.0 mg/dL (0.125 to 0.25 mmol/L) after resolution of volume depletion.	Volume depletion, and worsening HCM. May be useful in patients at risk for volume overload/congestive heart failure.
Salmon Calcitonin/CT 4 to 8 units/kg Intramuscular or SQ every 6 to 12 hours for 48 to 72 hours.	Inhibits bone resorption by interfering with osteoclast function. Promotes urinary calcium excretion, as well as that of magnesium, sodium, potassium and phosphate.	4 to 6 hours	6 to 8 hours. Rapidly lowers calcium by 1 to 2 mg/dL (0.25 to 0.50 mmol/L).	Tachyphylaxis may occur after 48 to 72 hours.
Bisphosphonates/BPs	Pamidronate and zoledronic acid are nitrogen-containing BPs that inhibit bone resorption by inhibiting farnesyl pyrophosphate synthase (FPPS) within osteoclasts to cause osteoclast apoptosis. They also interfere with osteoclast recruitment and function.			
Pamidronate/APD 60 to 90 mg IV over 2 to 24 hours. Can be repeated every 2 to 3 weeks.		48 to 72 hours	7 to 14 days; may last 2 to 4 weeks. Normalizes calcium in 60% to 70% of patients.	May cause kidney damage especially if glomerular filtration rate <30 to 35 mL/ minute. Acute-phase response relatively common; hypocalcemia; renal insufficiency possible if decreased glomerular filtration rate; Atypical femoral fractures are rare and ONJ occurs infrequently.
Zoledronic acid/ZLN 3 to 4 mg IV over 15 to 30 minutes. Can be repeated in 7 days, if desirable calcium level not achieved, and every 3 to 4 weeks thereafter.		48 to 72 hours	4 to 6 weeks. Normalizes calcium in 80% to 90% of patients.	May cause kidney damage especially if glomerular filtration rate <30 to 35 mL/ minute. Dose adjustment required if glomerular filtration rate <60 mL/min, and administer over 30 to 60 minutes.
Glucocorticoids 200 to 400 mg hydrocortisone IV/day for 3 to 5 days. 60 mg/day of prednisone for 10 days, or 10 to 20 mg/day for 7 days.	Decrease intestinal calcium absorption. Inhibits 1α-hydroxylase and limits 1,25-dihydroxyvitamin D production by mononuclear cells in patients with granulomatous diseases or lymphoma.	2 to 5 days	As long as on therapy.	Hyperglycemia, altered mental status, and hypertension.
Denosumab/Dmab 120 mg SQ. Repeat 1, 2 and 4 weeks later, then monthly thereafter.	Inhibits bone resorption via inhibition of RANKL. Dmab is an antibody to RANKL. Upon binding to RANKL, Dmab blocks the interaction between osteoclast surfaces) and prevents osteoclast formation and thus bone resorption.	3 to 10 days	Time to complete response 23 days. Median duration of effect 104 days. Normalizes calcium in at least	Acute-phase response rare; Atypical femoral fractures are rare and ONJ occurs infrequently. Rebound osteoclastogenesis discontinuation. Patients with GFR < 30 mL/ min have a higher risk of hypocalcemia, and a lower dose should be considered.
Calcimimetics Oral: Initial: 30 mg twice daily; increase dose incrementally every 2 to 4 weeks (to 60 mg twice daily, 90 mg twice daily, and 90 mg 3 to 4 times daily) as necessary to normalize SCa levels.	Calcium-sensing receptor agonist, reduces parathyroid hormone secretion, and may decrease renal calcium reabsorption.	2 to 3 days	During therapy. Reduces calcium by at least 1 mg/dL (0.25 mmol/L) in approximately 60% of patients.	Nausea, vomiting, headache, and fractures. Case reports indicate reduction of calcium levels in patients with refractory HCM related to non–small-cell lung, neuroendocrine, breast, or renal cancer.

Source: Information on mode of action, onset of action and duration of effect obtained in part from Lexicomp© Copyright 1978-2021, or relevant papers cited from Chakhtoura M, El-Hajj Fuleihan G. *Endocrinol Metab Clin North Am,* 2021; 50(4): 781-792 (15) and Guise T and Wysolmerski J. *N Engl J Med,* 2002;386:1443-1451. (16).
Abbreviations: HCM, hypercalcemia of malignancy; IV, intravenous; ONJ, osteonecrosis of the jaw; RANK, receptor activator of nuclear factor κ-B; RANKL, receptor activator of nuclear factor κ-B ligand; SQ, subcutaneous.
*Loop diuretics should not be used routinely. However, in patients with renal insufficiency or heart failure, judicious use of loop diuretics may be required to prevent fluid overload during saline hydration.

El-Hajj Fuleihan G et al. J Clin Endocrinol Metab 2023. PMID: 36545746.

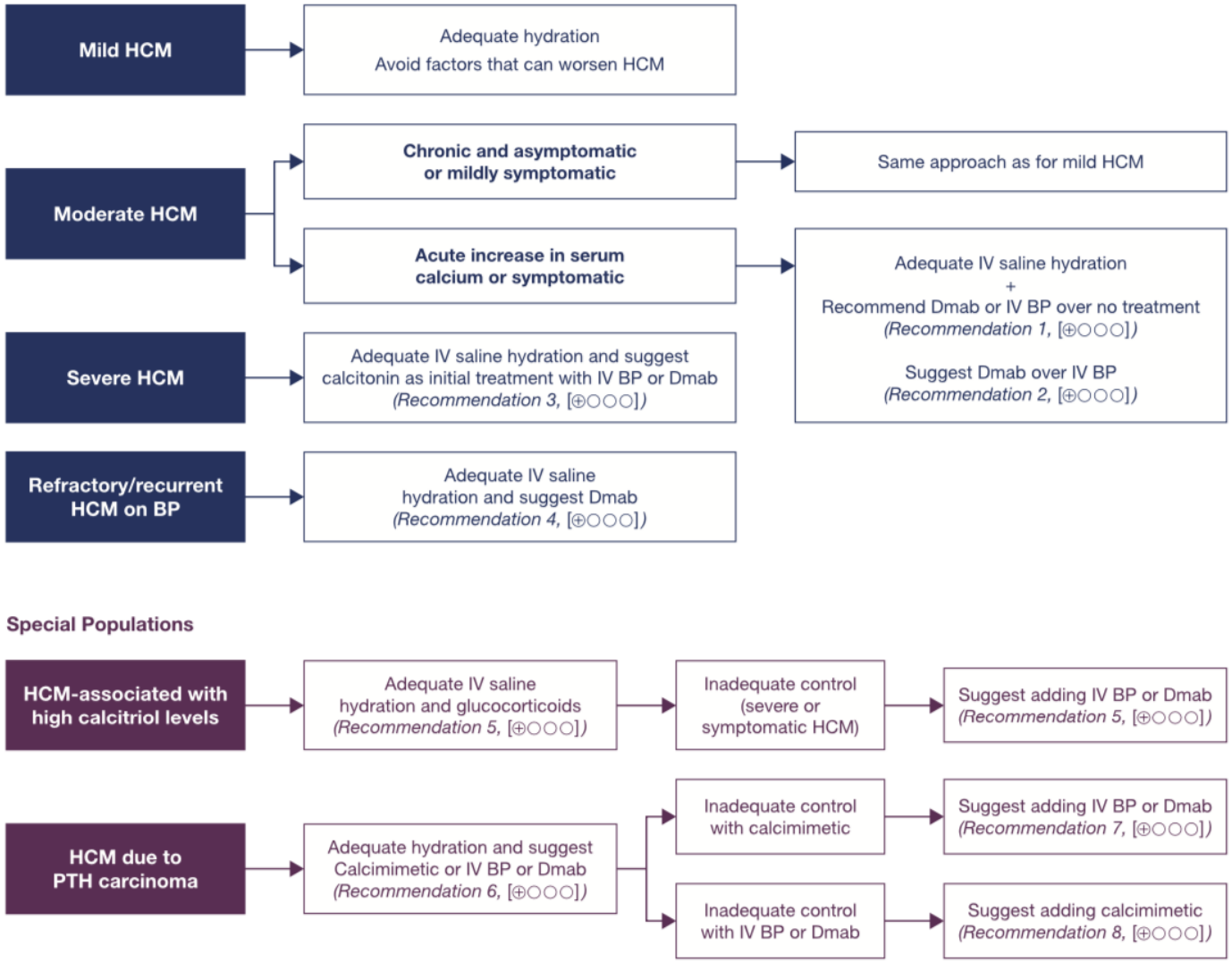


Figure 2. Suggested workflow for the management of HCM. The therapeutic approach depends upon the pathophysiology and severity of hypercalcemia and the rapidity of serum calcium increase. The severity of hypercalcemia is classified as the following: mild, albumin-adjusted SCa < 12 mg/dL (<3 mmol/L); moderate, albumin-adjusted SCa 12 to 14 mg/dL (3 to 3.5 mmol/L; Severe, albumin-adjusted SCa > 14 mg/dL; (>3.5 mmol/L). The ungraded good practice statements are listed below (see Table 2) and various recommendations are detailed in the main text. *Refer to the full EtDs and recommendations for additional considerations behind the recommendations. Abbreviations: HCM, hypercalcemia of malignancy; IV, intravenous; Dmab, Denosumab; IV BP, intravenous bisphosphonate; SCa, serum calcium.

สรุป Management

- **Specific treatment** – treatment according to the etiology of hypercalcemia
- **Supportive treatment** – hypercalcemia

El-Hajj Fuleihan G et al. J Clin Endocrinol Metab 2023. PMID: 36545746.

Primary Hyperparathyroidism

REVIEW

JBMR®

Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop

John P. Bilezikian,[1] Aliya A. Khan,[2] Shonni J. Silverberg,[1] Ghada El-Hajj Fuleihan,[3] Claudio Marcocci,[4] Salvatore Minisola,[5] Nancy Perrier,[6] Antonio Sitges-Serra,[7] Rajesh V. Thakker,[8] Gordon Guyatt,[9] Michael Mannstadt,[10] John T. Potts,[10] Bart L. Clarke,[11] and Maria Luisa Brandi,[12] On behalf of the International Workshop on Primary Hyperparathyroidism

Bilezikian JP et al. J Bone Miner Res 2022. PMID: 36245251.

1. **How should primary hyperparathyroidism (PHPT) be diagnosed?**
   - 1.1. Hypercalcemic PHPT: an elevated serum calcium adjusted for albumin in the presence of an elevated or inappropriately normal intact parathyroid hormone (PTH) (utilizing either a second or third generation assay) on two occasions at least 2 weeks apart.
   - 1.2. What is the differential diagnosis of hypercalcemia and elevated levels of PTH?
     - 1.2.1. Familial hypocalciuric hypercalcemia (FHH) may be suspected in younger individuals with a urinary calcium /creatinine clearance ratio <0.01 and/or those with a family history of hypercalcemia.
     - 1.2.2. Thiazide diuretics and lithium (see text)
     - 1.2.3. Ectopic secretion of PTH (very rare)
   - 1.3. Normocalcemic PHPT: normal adjusted total calcium and normal ionized calcium levels along with elevated intact PTH (utilizing either a second or third generation assay) on at least two occasions over 3–6 months after all alternative causes for secondary hyperparathyroidism have been ruled out.

A summary of panel recommendations for evaluation

Biochemical:

1. Measure adjusted total serum calcium (ionized if NPHPT is a consideration), phosphorus, intact PTH, 25OHD, creatinine

Skeletal:

2. Three-site DXA (lumbar spine, hip, distal 1/3 radius); imaging for vertebral fractures (VFA or vertebral X-rays). As an adjunctive test, the TBS can be helpful if available.

Renal:

3. eGFR or, preferably, creatinine clearance, full 24-hour urinary calcium. Imaging for nephrolithiasis/nephrocalcinosis. In those with hypercalciuria, a stone risk profile is recommended. In those with stones (an indication for surgery) a stone risk profile is recommended whether or not the patient has hypercalciuria.

Bilezikian JP et al. J Bone Miner Res 2022. PMID: 36245251.

2. **What are the clinical phenotypes of PHPT?**

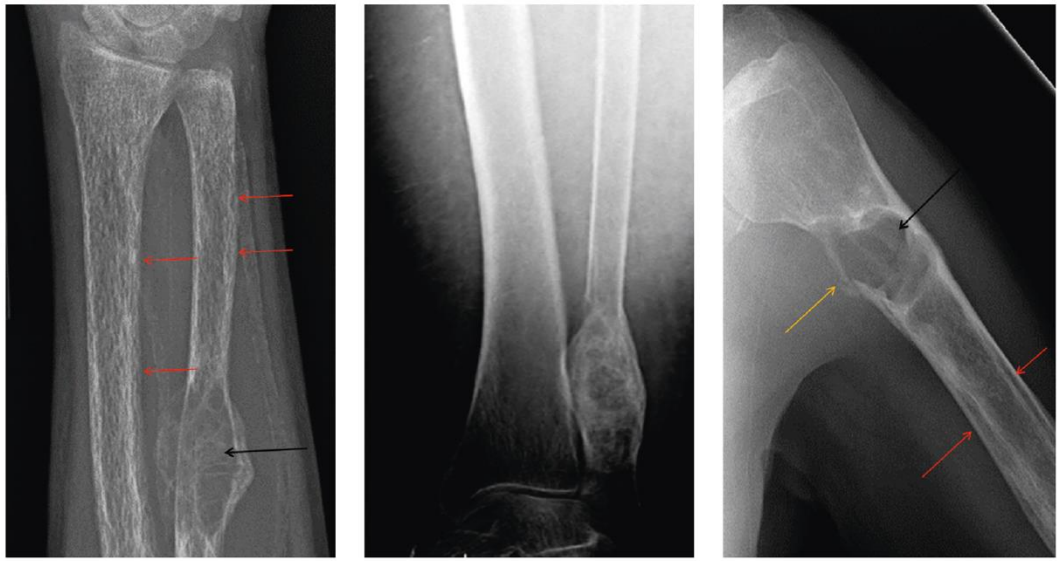
2.1. Symptomatic PHPT: associated with overt skeletal and renal complications that may include osteitis fibrosa cystica and/or fractures, chronic kidney disease, nephrolithiasis and/or nephrocalcinosis

2.2. Asymptomatic PHPT: no overt symptoms or signs; typically discovered by biochemical screening. Two forms of asymptomatic PHPT are defined after evaluation:

2.2.1. with target organ involvement

2.2.2. without target organ involvement

2.3. Normocalcemic PHPT: Skeletal or renal complications may or may not exist in those whose presentation fits this definition.



Brown tumors

Bilezikian JP et al. J Bone Miner Res 2022. PMID: 36245251.
Image from Bennett J et al. Int J Endocrinol 2020. PMID: 32148487.

6. **What is the role of preoperative imaging and intraoperative PTH measurements? Panel recommendations**

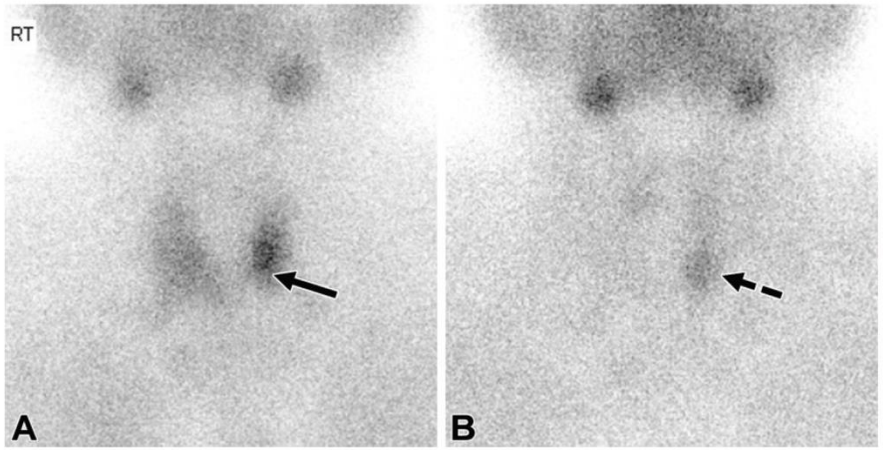
6.1. Preoperative imaging is not recommended for diagnostic purposes.

6.2. Preoperative imaging is recommended for those who are going to have parathyroid surgery in order to locate the abnormal parathyroid gland(s).

6.3. Preoperative imaging modalities include high resolution neck ultrasound, technetium-99 m-sestamibi subtraction scintigraphy, and contrast-enhanced four-dimensional (4D) computed tomography (CT).

6.4. With successful preoperative imaging, selective parathyroidectomy, combined or not with intraoperative PTH monitoring, achieves high cure rates in the hands of experienced surgeons.

6.5. Advantages of the selective approach include: shorter operative time, less tissue scarring, less risk to



(A) Early anterior small–field-of-view *planar scintigram of the neck 10 minutes after 99mTc-sestamibi administration shows increased thyroid gland uptake, with a focus of more significant uptake (arrow) overlying the left thyroid lobe.* ***(B) Delayed anterior small–field-of-view*** *planar scintigram of the neck 90 minutes after 99mTc-sestamibi administration shows corresponding washout from the thyroid gland and retention of activity (arrow) overlying the left thyroid lobe.*

Bilezikian JP et al. J Bone Miner Res 2022. PMID: 36245251.
Image from Naik M et al. Radiographics 2022. PMID: 35427174.

4. **What are the indications and role for surgical management of asymptomatic PHPT? (GRADEd Recommendation)**

In patients with asymptomatic PHPT, we recommend surgery to cure the disease (strong recommendation/high quality evidence).

Table 2. Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism: A Comparison of Current Recommendations with Previous Ones

Parameter	1990	2002	2008	2013	2022
Serum Calcium (>upper limit of normal)	1–1.6 mg/dL (0.25–0.4 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)
Skeletal	BMD by DXA: *Z*-score < −2.0 (site unspecified)	BMD by DXA: *T*-score < −2.5 at any site	BMD by DXA: *T*-score < −2.5 at any site Previous fragility fracture	a. BMD by DXA: *T*-score < −2.5 at lumbar spine, total hip, femoral neck or distal 1/3 radius b. Vertebral fracture by X-ray, CT, MRI, or VFA	a. BMD by DXA: *T*-score < −2.5 at lumbar spine, total hip, femoral neck or distal 1/3 radius* b.Vertebral fracture by X-ray, CT, MRI or VFA
Renal	a. eGFR reduced by >30% from expected. b. 24-Hour urine for calcium >400 mg/day (>10 mmol/day)	a. eGFR reduced by >30% from expected b. 24-Hour urine for calcium >400 mg/day (>10 mmol/day)	a. eGFR <60 cc/min b. 24-Hour urine for calcium not recommended	a. eGFR <60 cc/min b. 24-hour urine for calcium >400 mg/day (>10 mmol/day) and increased stone risk by biochemical stone risk analysis c. Presence of nephrolithiasis or nephrocalcinosis by X-ray, ultrasound, or CT	a. eGFR <60 cc/min** b. Complete 24-hour urine for calcium >250 mg/day in women (>6.25 mmol/day) or > 300 mg/day in men (>7.5 mmol/day) c. Presence of nephrolithiasis or nephrocalcinosis by X-ray, ultrasound, or CT
Age	<50 years	<50 years	<50 years	<50 years	<50 years

This table does not include the clearcut indication for surgery in anyone who has symptomatic PHPT (marked hypercalcemia, kidney stones, fractures). Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible and also in patients opting for surgery, in the absence of meeting any guidelines, as long as there are no medical contraindications. Patients need meet only one of these criteria to be advised to have parathyroid surgery. They do not have to meet more than one.

*Consistent with the position established by ISCD the use of *Z*-scores instead of *T*-scores is recommended in evaluating BMD in premenopausal women and men younger than 50 years.[174] These individuals meet criteria for surgery by virtue of age.

**Special consideration might be justified in those whose eGFR is >60 cc/min but in whom there is only one kidney. In those situations, parathyroidectomy could be considered to be special indication for surgery.

Bilezikian JP et al. J Bone Miner Res 2022. PMID: 36245251.

A summary of panel recommendations for surgical management of PHPT

1. Symptomatic PHPT: all symptomatic patients should be offered parathyroid surgery unless medically contraindicated.
2. Asymptomatic PHPT
   A. Serum calcium >1 mg/dL (0.25 mmol/L) above the upper limit of normal
   B. Skeletal involvement:
      a. A fracture by VFA or vertebral X-ray or
      b. BMD by *T*-score ≤ −2.5 at any site or
   C. Renal involvement:
      a. eGFR or creatinine clearance <60 mL/min or
      b. Nephrocalcinosis or nephrolithiasis by X-ray, ultrasound, or other imaging modality or
      c. Urinary calcium excretion: hypercalciuria (eg, >250 mg/day in women; >300 mg/day in men).
   D. Age <50 years (no other indications are necessary; age <50 years is a sufficient indication)
   E. If no aforementioned guidelines are met, PTX is still an option with concurrence of the patient and physician and if there are no contraindications

ถ้าไม่ผ่าตัด

Panel recommendations for surgery among those with hypercalcemia who are being monitored (ungraded)

1. Serum calcium becomes consistently >1 mg/dL (0.25 mmol/L) above the upper limit of normal or
2. A nontraumatic fracture or
3. A kidney stone or
4. A significant reduction in BMD (> the least significant change of the measurement and to a *T*-score ≤ −2.5) or
5. A significant reduction in creatinine clearance (averaging >3 mL/min over a 1-year to 2-year period) to <60 cc/min if associated with other changes that indicate progression.

Bilezikian JP et al. J Bone Miner Res 2022. PMID: 36245251.

Medical Therapy in Primary Hyperparathyroidism

Summary of panel recommendations for nutritional and pharmacological management of PHPT in those not to undergo parathyroid surgery (GRADEd)

1. In patients with PHPT who do not undergo PTX, pharmacological management should be used only for specific indications.
   a. In patients with low BMD who do not undergo PTX, we suggest bisphosphonates (eg, alendronate) or denosumab (weak recommendation based on very low-quality evidence)
   b. In patients with PHPT and serum calcium levels >11.0 mg/dL (>0.25 mmol/L) above the upper limit of normal who do not undergo PTX, we suggest cinacalcet (weak recommendation based on low quality of evidence)
2. In patients with PHPT and vitamin D insufficiency (25OH vitamin D <30 ng/mL (75 nmol/L) or deficiency (<12 ng/mL; <30 nmol/L), we suggest vitamin D supplementation (weak recommendation based on very low-quality evidence)

Table 3. Trials Included in Systematic Review of Medical therapy[8]

Intervention	[Calcium] (mg/dL)	[PTH] (pg/mL)	Urinary Ca (mg/day)	Conclusions of systematic reviews (effect on bone density*)	Conclusions of systematic reviews (effect on serum calcium)	References
Alendronate	11.0 ± 0.5	170 ± 95	204 ± 109	Increases bone mineral density**	No effect	Chow and colleagues[193]; Khan and colleagues[190]; Rossini and colleagues[194]
Estrogen (raloxifene data are sparse)	10.6 ± 0.16	149 ± 32	240 ± 41	Increases bone mineral density***	Reduced***	Grey and colleagues[197]; Rubin and colleagues[198]
Cinacalcet	11.2 ± 0.45	138 ± 46	290.0 ± 120	No effect	Reduced**	Khan and colleagues[202]; Peacock and colleagues[201]
Denosumab	10.9 ± 0.1	115 ± 16	NR	Increases bone mineral density	No effect	Leere and colleagues[205]
Vitamin D	11.0 ± 0.3	83 ± 15	376 (320–432)	Increases bone mineral** density***	No effect	Lind and colleagues[184]; Roglighed and colleagues[182,183]

NR = not reported.

Using GRADE methodology to reflect quality of available data: *There are no data documenting a direct effect on fracture incidence, associated with an increase in bone mineral density. **Medication "probably" effects outcome: moderate quality evidence. ***Medication "may" effect outcome: low quality evidence.

Bilezikian JP et al. J Bone Miner Res 2022. PMID: 36245251.

3.5. Genetic: genetic evaluation should be considered for patients <30 years old, those with multigland disease by history or imaging, and/or those with a family history of hypercalcemia and/or a syndromic disease

MEN1

- Primary hyperparathyroidism
- Pancreatic neuroendocrine tumor
- Pituitary adenoma
- Others, e.g., adrenal tumor, meningioma, etc.

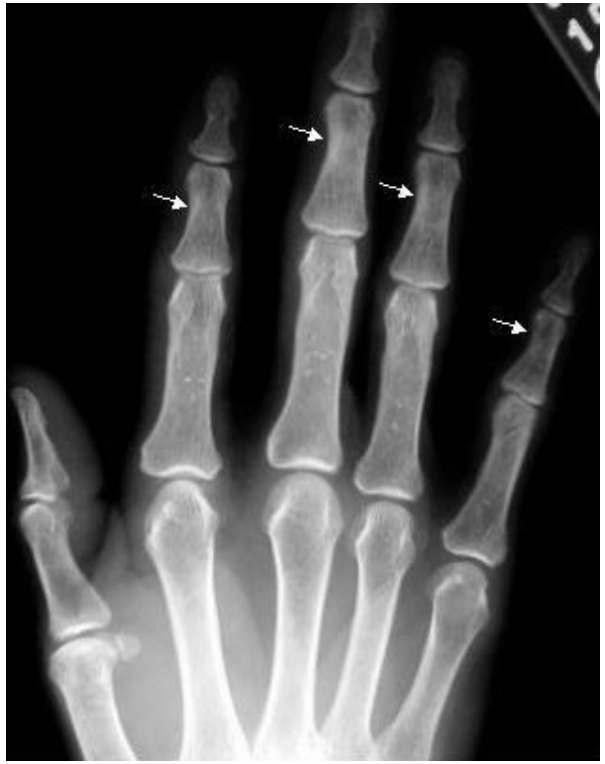
HOWEVER, being >30 years old **DOES NOT** rule out syndromic forms of familial PTHPT.

Genetics of PHPT

Studies of syndromic and nonsyndromic forms of familial PHPT have helped to identify genetic abnormalities involved in parathyroid tumorigenesis. More than 10% of patients with PHPT will have a mutation in one of 10 genes that have been implicated.[3,71] The genetics of PHPT are delineated in an accompanying report.[3] Testing for mutations in these genes, which is routinely available, can facilitate the diagnosis of a syndromic or nonsyndromic form of PHPT, and thereby help in the clinical management and treatment of PHPT patients and their relatives. Although confirmation of the clinical diagnosis of PHPT does not require genetic testing, and should not be a criterion for diagnosis, nevertheless, elucidation of genetic abnormalities can help in the following ways:

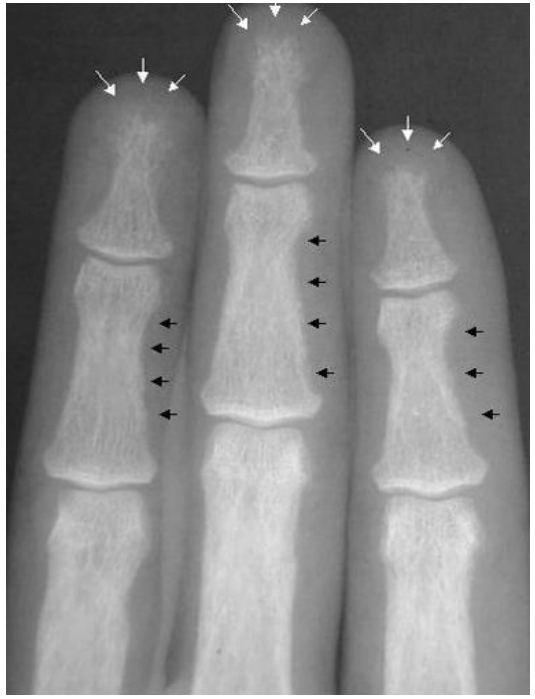
1. If the diagnosis is the hyperparathyroidism jaw tumor (HPT-JT) syndrome, early parathyroidectomy (bilateral exploration) is indicated because of the increased risk of parathyroid carcinoma.
2. If the diagnosis is multiple endocrine neoplasia type 1 (MEN1) or MEN2, a bilateral neck exploration is needed. Selective parathyroidectomy is contraindicated because of the presence of multiglandular disease in these patients.
3. In patients whose genetic testing reveals hypocalciuric hypercalcemia (FHH), surgery is contraindicated in most cases.
4. Genetic testing helps to identify family members who may or may not be at risk. Genetic counseling and evaluation, thus, should be considered for patients <30 years with PHPT, those with multigland disease by history or imaging, those with a family history of hypercalcemia or syndromic diseases such as MEN1, MEN2A, MEN4, or HPT-JT syndrome,[3,71] and in patients with atypical parathyroid adenoma and parathyroid carcinoma.[58,59]

Other Radiographic Features in Primary Hyperparathyroidism



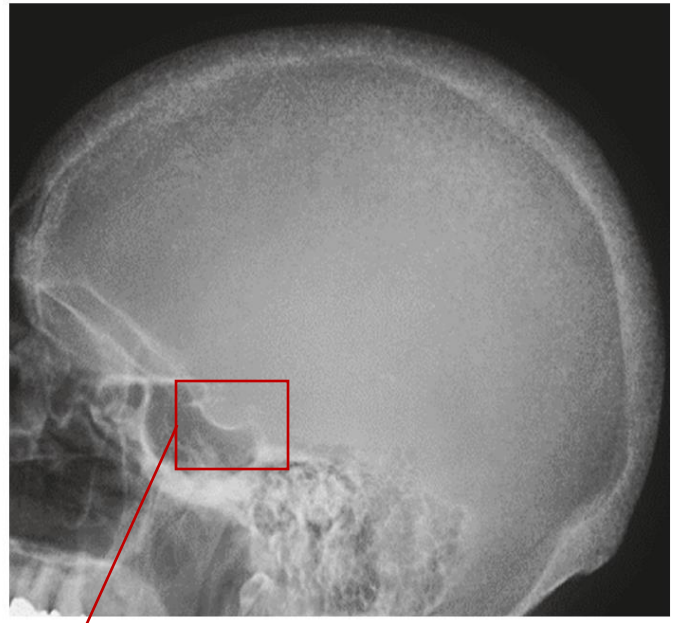
Middle phalanges

White arrows: ***Subperiosteal bone resorption*** along the radial aspects of the middle phalanges



Middle phalanges

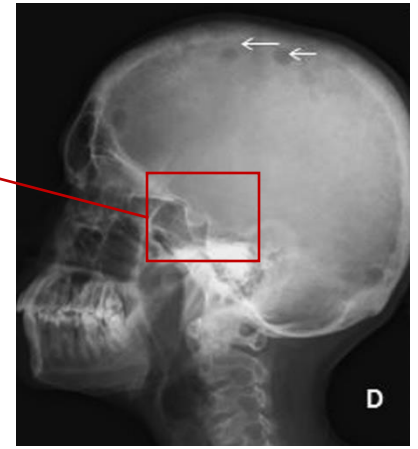
White arrows: ***Severe tuftal resorption***
Black arrows: Subperiosteal and intracortical resorption of the middle phalanges



Skull

"Salt and pepper appearance"

Always look for widening sella!



Skull

Pepper pot appearance

คำแนะนำเวชปฏิบัติ
การดูแลรักษาโรคกระดูกพรุน

มูลนิธิโรคกระดูกพรุนแห่งประเทศไทย พ.ศ. 2564

ข้อบ่งชี้ในการส่งตรวจความหนาแน่นของกระดูก

แนะนำส่งตรวจความหนาแน่นของกระดูกโดยอาศัยเกณฑ์อายุและปัจจัยเสี่ยงทางคลินิกข้อใดข้อหนึ่งต่อไปนี้

1. ผู้หญิงอายุ 65 ปีขึ้นไป และผู้ชายอายุ 70 ปีขึ้นไป
2. ผู้หญิงที่หมดประจำเดือนก่อนอายุ 45 ปี ซึ่งรวมถึงผู้ที่ถูกตัดรังไข่ทั้งสองข้าง
3. ผู้หญิงที่มีภาวะฮอร์โมนเอสโตรเจนต่ำ (hypoestrogenism) ต่อเนื่องนานกว่า 1 ปี ก่อนเข้าสู่วัยหมดประจำเดือน ซึ่งพบได้ในผู้ป่วยที่ได้รับ GnRH agonist หรือมี functional hypothalamic amenorrhea เช่น ผู้ป่วยโรคเรื้อรังทางอายุรกรรม คนที่ออกกำลังกายอย่างหนักเป็นเวลานาน เป็นต้น โดยยกเว้นกรณีตั้งครรภ์และให้นมบุตร
4. ผู้หญิงวัยหมดประจำเดือนที่มีอายุน้อยกว่า 65 ปี หรือผู้ชายที่มีอายุน้อยกว่า 70 ปี ที่มีความเสี่ยงข้อใดข้อหนึ่งดังต่อไปนี้
   - กำลังเริ่มยาหรือได้รับยา glucocorticoid ขนาดเทียบเท่าหรือมากกว่า prednisolone 5 มก./วัน ต่อเนื่องกันตั้งแต่ 3 เดือนขึ้นไป
   - มีบิดาหรือมารดากระดูกสะโพกหักจากอุบัติเหตุที่ไม่รุนแรง
   - ดัชนีมวลกายน้อยกว่า 20 กก./ตร.ม.
   - ส่วนสูงลดลงตั้งแต่ 4 ซม.ขึ้นไป เมื่อเทียบกับประวัติส่วนสูงสูงสุดของผู้ป่วย หรือตั้งแต่ 2 ซม.ขึ้นไปจากบันทึกการวัดส่วนสูง 2 ครั้ง
   - ผู้หญิงที่ได้รับการรักษาด้วย aromatase inhibitor หรือผู้ชายที่ได้รับการรักษาด้วย androgen deprivation therapy
   - ภาพถ่ายรังสีแสดงลักษณะ radiographic osteopenia หรือกระดูกสันหลังผิดรูปจาก vertebral fracture
   - มีประวัติกระดูกหักจากอุบัติเหตุไม่รุนแรง (fragility fracture)
5. ก่อนเริ่มยารักษาโรคกระดูกพรุน และติดตามผลที่ 1-2 ปีหลังการรักษา

หัวข้อที่ 1: คำแนะนำการวินิจฉัยโรคกระดูกพรุนและแนวทางการตรวจเพิ่มเติม (คำแนะนำข้อที่ 1-5)

ข้อที่	คำแนะนำ	น้ำหนักคำแนะนำ	คุณภาพหลักฐาน
1	เกณฑ์การวินิจฉัยโรคกระดูกพรุนประกอบด้วยข้อใดข้อหนึ่งต่อไปนี้		
	1. กระดูกสันหลังหักหรือกระดูกสะโพกหัก อันเนื่องมาจากอุบัติเหตุที่ไม่รุนแรง	I	B
	2. ค่า T-score น้อยกว่าหรือเท่ากับ -2.5 ที่ตำแหน่ง lumbar spine, total hip, femoral neck หรือ 1/3 radius*	I	B
	3. ค่า T-score ระหว่าง -1.0 และ -2.5 ร่วมกับความเสี่ยงต่อการเกิดกระดูกสะโพกหักในช่วงเวลา 10 ปี ซึ่งประเมินโดย FRAX** สำหรับประเทศไทย มีค่ามากกว่าหรือเท่ากับร้อยละ 3	IIa	B
	4. ค่า T-score ระหว่าง -1.0 และ -2.5 ร่วมกับมีกระดูกหักในตำแหน่ง proximal humerus, pelvis หรือ forearm จากอุบัติเหตุที่ไม่รุนแรง	IIa	C
2	ต้องวินิจฉัยแยกโรคกับ metabolic bone disease อื่น ๆ ก่อนให้การวินิจฉัยโรคกระดูกพรุน	I	B
3	ควรตรวจหาสาเหตุทุติยภูมิของโรคกระดูกพรุนและให้การดูแลรักษาร่วมกัน	I	B

หัวข้อที่ 5: คำแนะนำการรักษาด้วยยารักษาโรคกระดูกพรุน

หัวข้อที่ 5.1: ข้อบ่งชี้การใช้ยารักษาโรคกระดูกพรุน (คำแนะนำข้อที่ 29)

ข้อที่	คำแนะนำ	น้ำหนักคำแนะนำ	คุณภาพหลักฐาน
29	ข้อบ่งชี้ในการใช้ยารักษาโรคกระดูกพรุน ประกอบด้วยข้อใดข้อหนึ่งต่อไปนี้		
	- มีกระดูกสันหลังหัก หรือกระดูกสะโพกหักจากโรคกระดูกพรุน	I	A
	- T-score น้อยกว่าหรือเท่ากับ -2.5*	I	A
	- T-score ระหว่าง -1.0 และ -2.5* ร่วมกับความเสี่ยงต่อการเกิดกระดูกสะโพกหักในช่วงเวลา 10 ปี ซึ่งประเมินโดย FRAX สำหรับประเทศไทย มีค่ามากกว่าหรือเท่ากับร้อยละ 3	IIa	C
	- T-score ระหว่าง -1.0 และ -2.5* ร่วมกับมีกระดูกหักจากโรคกระดูกพรุนในตำแหน่งอื่นที่ไม่ใช่กระดูกสันหลังและกระดูกสะโพก ได้แก่ กระดูกหักในตำแหน่ง proximal humerus, pelvis หรือ forearm	IIb	C

* การตรวจความหนาแน่นของกระดูกต้องตรวจด้วยเครื่อง central dual energy X-ray absorptiometry (DXA) มาตรฐานเท่านั้นแนะนำให้ใช้ค่า T-score ที่ตำแหน่ง lumbar spine, femoral neck หรือ total hip เป็นหลัก อาจจะพิจารณาใช้ค่า T-score ที่ตำแหน่ง 1/3 radius ได้ ในกรณีที่ไม่สามารถส่งตรวจหรือแปลผลการตรวจที่ตำแหน่งกระดูกสันหลัง หรือกระดูกสะโพกได้เท่านั้น

Etiology of Hypocalcemia

Parathyroid-Related Disorders

Absence of the Parathyroid Glands or of PTH

Congenital
- DiGeorge syndrome
- X-linked or autosomally inherited hypoparathyroidism
- Autoimmune polyglandular syndrome type I
- PTH gene mutations

Postsurgical hypoparathyroidism

Infiltrative disorders
- Hemochromatosis
- Wilson disease
- Metastases

Hypoparathyroidism post radioactive iodine thyroid ablation

Impaired Secretion of PTH

Hypomagnesemia

Respiratory alkalosis

Activating mutations of the calcium sensor or *GNA11*

Target Organ Resistance

Hypomagnesemia

Pseudohypoparathyroidism
- Type I
- Type II

Vitamin D-Related Disorders

Vitamin D deficiency
- Dietary absence
- Malabsorption

Accelerated loss
- Impaired enterohepatic recirculation
- Anticonvulsant medications
- CYP3A4 mutation

Impaired 25 hydroxylation
- Liver disease
- Isoniazid
- *CYP2R1* mutation

Impaired 1α-hydroxylation
- Renal failure

Vitamin D–dependent rickets, type I

Oncogenic osteomalacia

Target organ resistance
- Vitamin D–dependent rickets, type II
- Phenytoin

Other Causes

Excessive deposition into the skeleton
- Osteoblastic malignancies
- Hungry bone syndrome

Impaired bone resorption
- Vitamin D deficiency
- Bisphosphonates
- RANKL inhibition

Chelation
- Foscarnet
- Phosphate infusion
- Infusion of citrated blood products
- Infusion of EDTA containing contrast reagents
- Fluoride

Neonatal hypocalcemia
- Prematurity
- Asphyxia
- Diabetic mother
- Hyperparathyroid mother
- Vitamin D–deficient mother
- Infantile malignant osteopetrosis

HIV
- Drug therapy
- Vitamin D deficiency
- Hypomagnesemia
- Impaired PTH responsiveness

Critical illness
- Pancreatitis
- Toxic shock syndrome
- Intensive care unit patients

CYP2R1, Cytochrome P450, family 2, subfamily R, member 1; *CYP3A4*, cytochrome P450, family 3, subfamily A, member 4; *EDTA*, ethylenediaminetetraacetic acid; *GNA11*, G protein subunit alpha 11; *PTH*, parathyroid hormone; *RANKL*, receptor activator of nuclear factor κB ligand; *X*, X chromosome.

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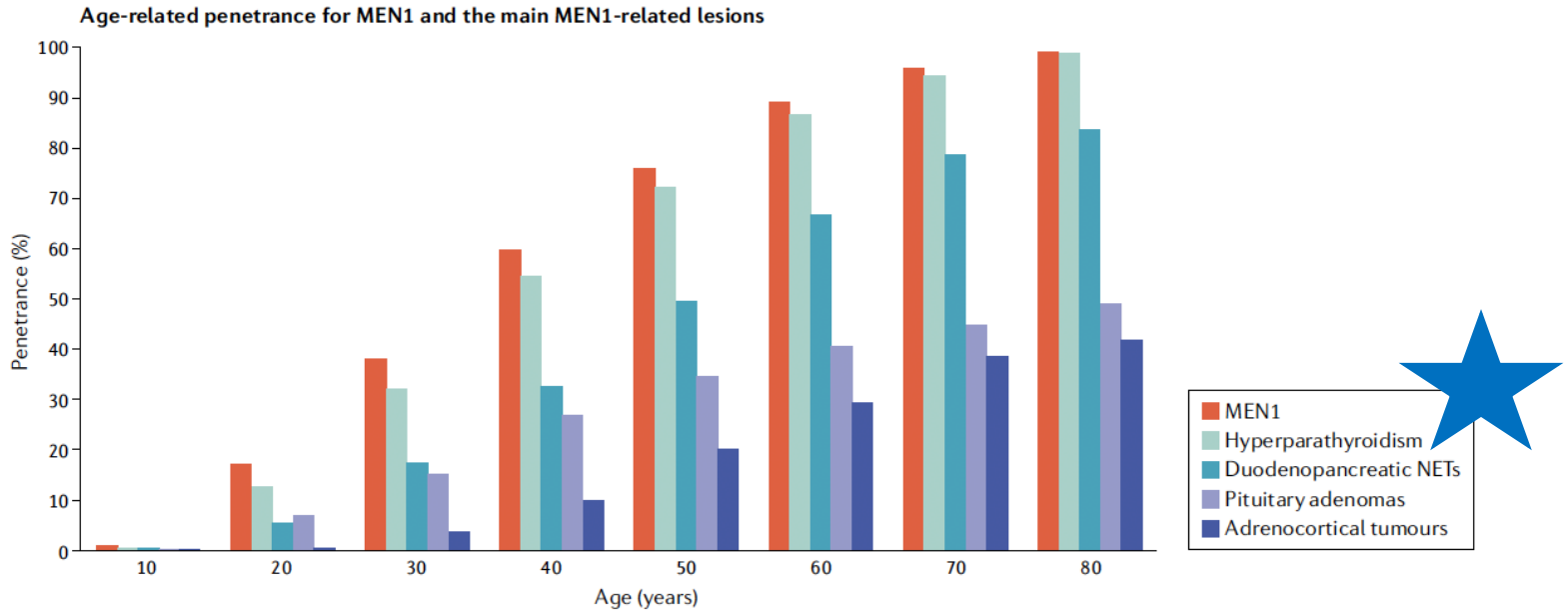
MEN1 and common tumors

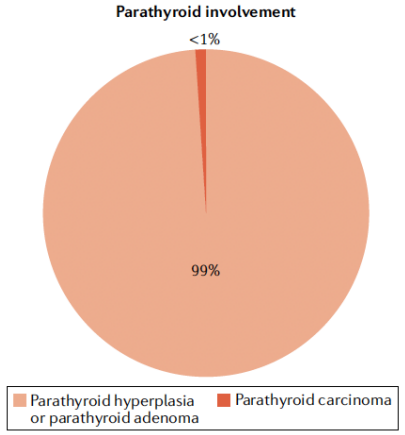
Prolactinoma

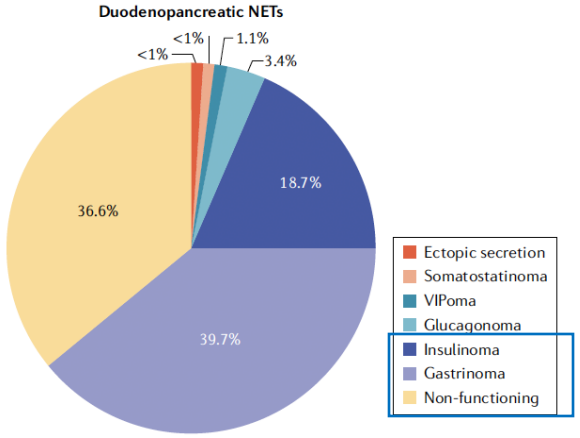
Acromegaly

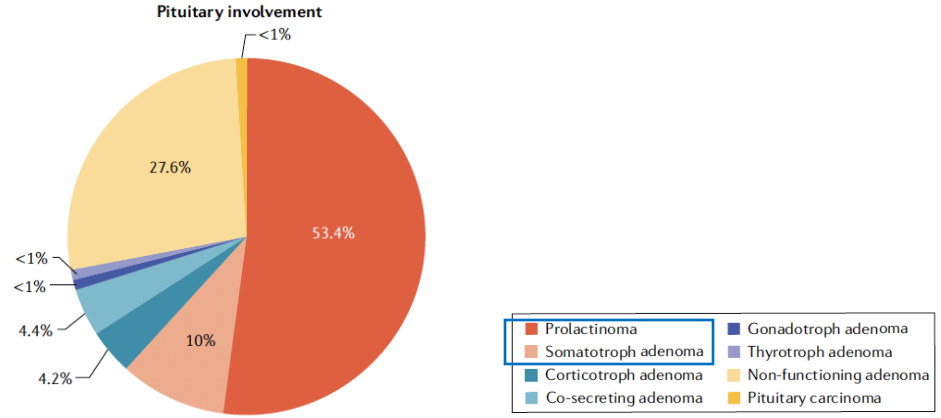
Multiple Neuroendocrine Neoplasm Type1 (MEN1)



Primary hyperparathyroidism เป็นตัวเอก!!







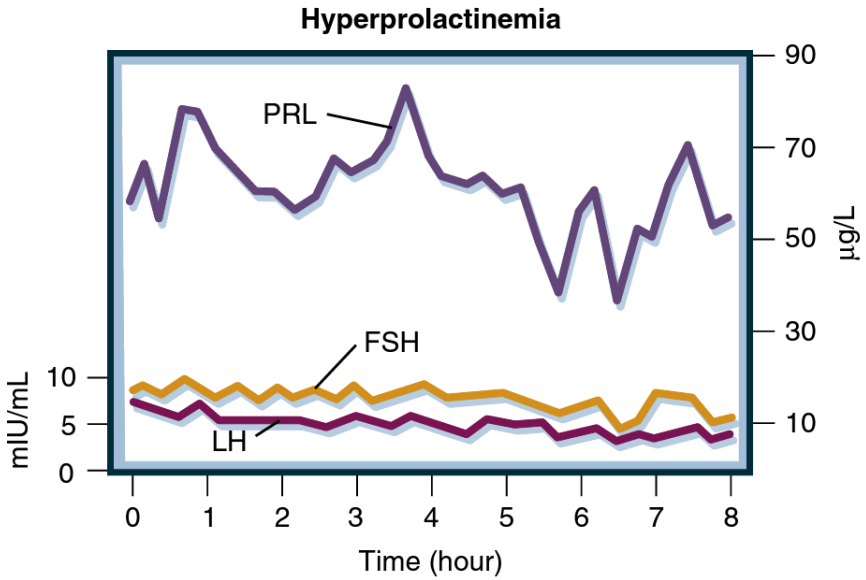
Prolactinoma: Signs & Symptoms

Associated with hyperprolactinemia

- Amenorrhea, oligomenorrhea
- Infertility
- Decreased libido, impotence, premature ejaculation, oligospermia
- Galactorrhea
- Osteoporosis

Associated with tumor mass

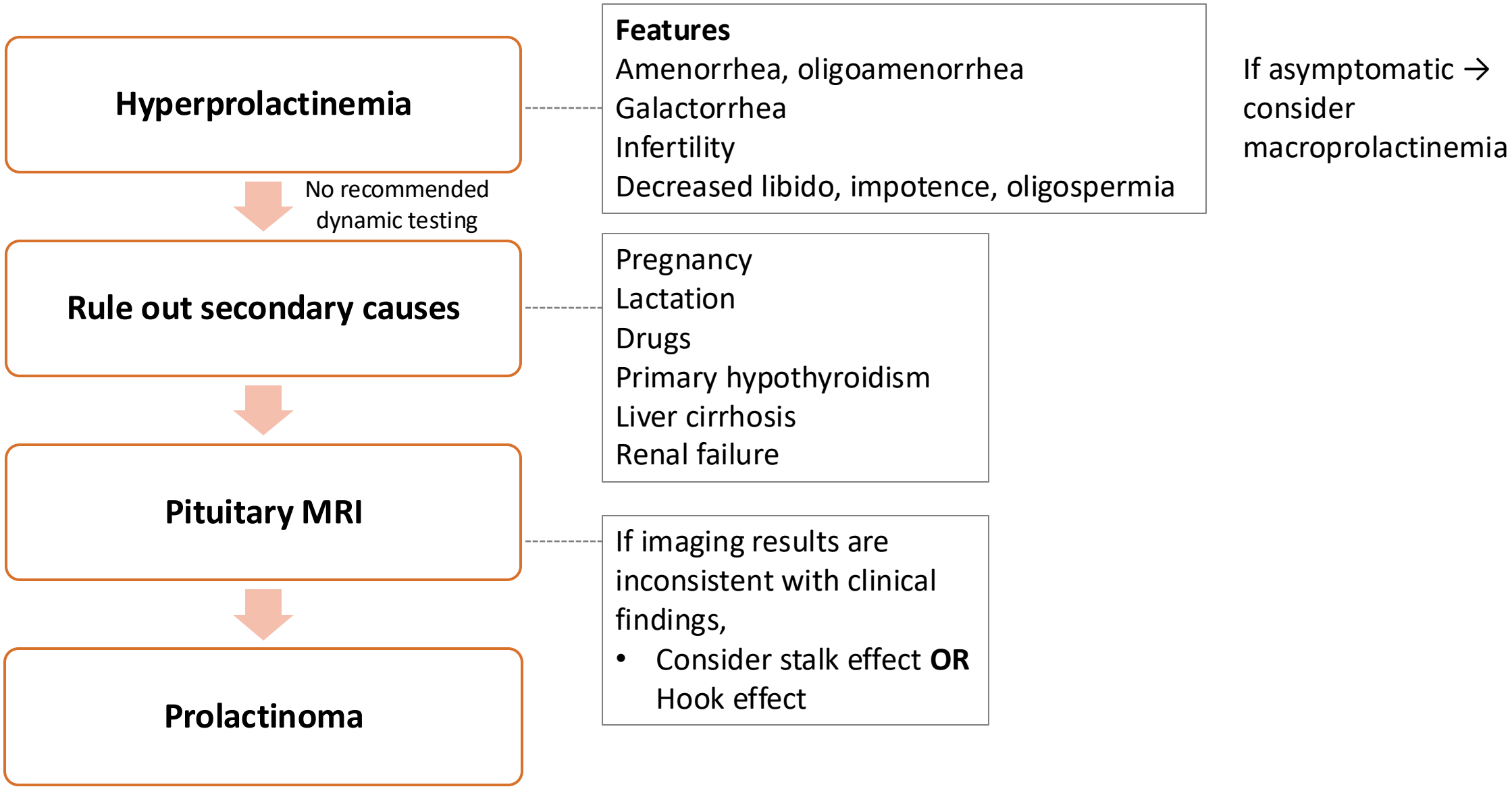
- Visual field abnormalities
- Blurred vision or decreased visual acuity
- Hypopituitarism
- Headaches
- Cranial nerve palsies
- Pituitary apoplexy



PRL, prolactin; FSH, follicle stimulating hormone; LH, luteinizing hormone

Image from Williams textbook of Endocrinology 14th edition

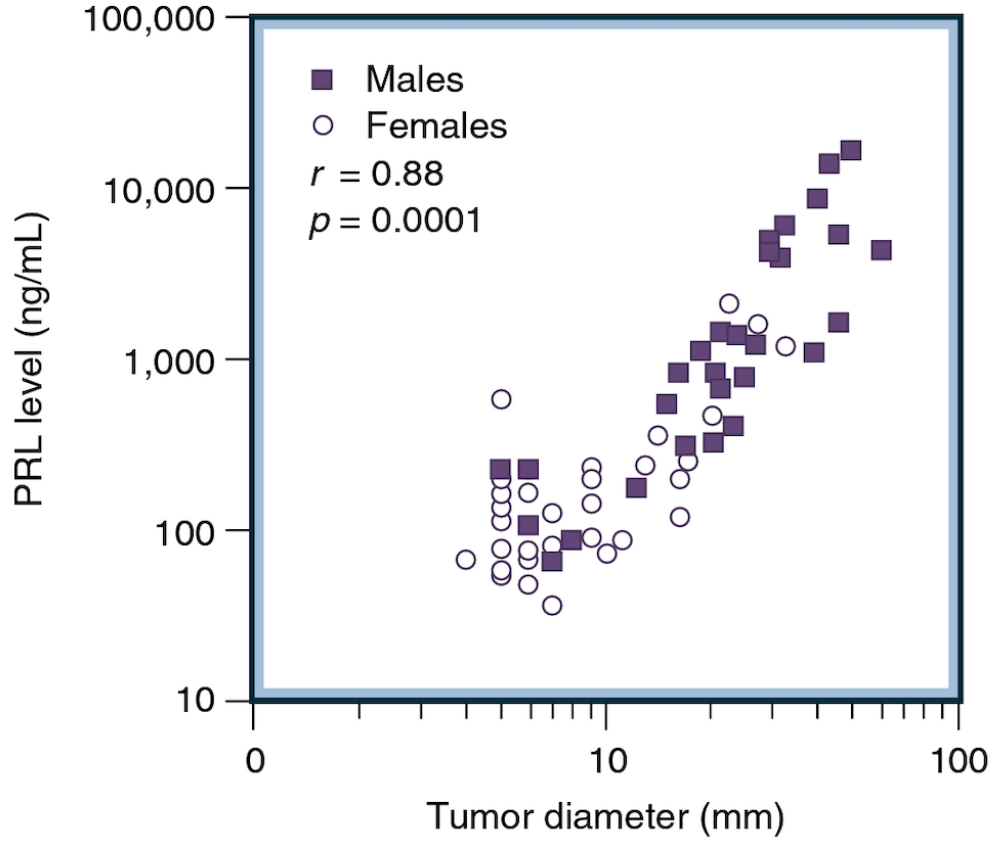
Approach to Patients with Hyperprolactinemia



Prolactinoma

- Prolactinomas are classified by their size
  - Size <1 cm: microprolactinoma
  - Size ≥1 cm: macroprolactinoma
  - ***Size >4 cm: giant prolactinoma***

- Macroprolactinomas have a greater propensity to grow & tumor size correlates with serum PRL levels.



Serum PRL level & tumor size

Adapted from Danila DC, Klibanski A. Prolactin secreting pituitary tumors in men. Endocrinologist. 2001; 11:105-111.
Williams Textbook of Endocrinology 14th edition

Size & Prolactin Levels in Prolactinomas

- Prolactinomas can present with any level of PRL elevation
  - PRL levels range from minimal elevation-hundreds in macroprolactinomas.
- PRL level >200 μg/L = strongly indicative of a PRL-secreting pituitary tumor
  - However, it could result from some drugs, e.g., metoclopramide, risperidone, and phenothiazines.
    - When suspecting drug-induced hyperprolactinemia → withhold medication for ≥3 days and retest PRL.
- PRL >500 μg/L = only observed in prolactinomas

Vilar L et al. Diagnosis and management of hyperprolactinemia: results of a Brazilian multicenter study with 1234 patients. J Endocrinol Invest. 2008 May;31(5):436-44.
Arafah BM, Nekl KE, Gold RS, Selman WR. Dynamics of prolactin secretion in patients with hypopituitarism and pituitary macroadenomas. J Clin Endocrinol Metab. 1995 Dec;80(12):3507-12.
Melmed S et al. J Clin Endocrinol Metab 2011. PMID: 21296991.
Williams Textbook of Endocrinology 14th edition

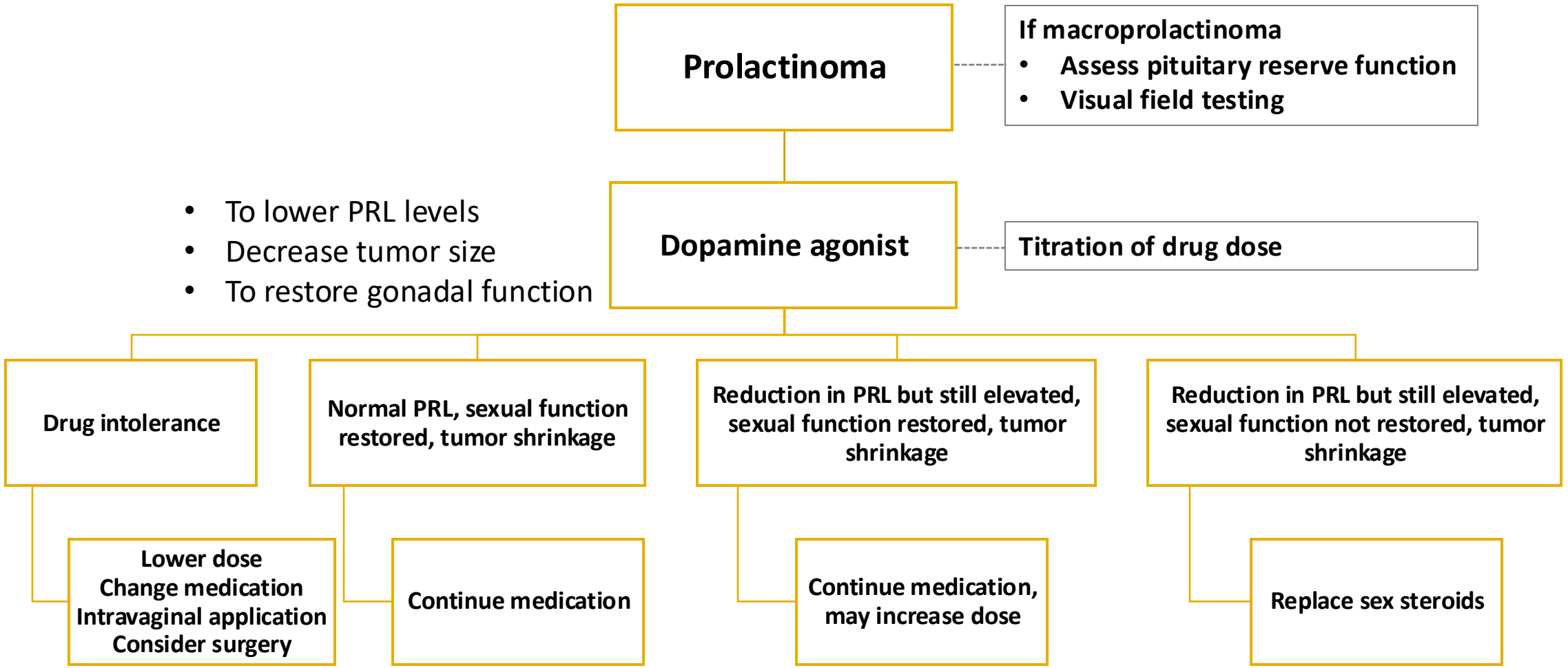
Size & Prolactin Levels in Prolactinomas

- If PRL <200 μg/L in the presence of pituitary macroadenoma
  - Consider stalk effects
  - Macroprolactinemia can also occur with pituitary adenoma

- However, patients with small macroadenoma + PRL ~ 200 μg/L
  - It is prudent to first treat medically
    - If the tumor shrinks → prolactinoma
    - If the tumor does not shrink → the mass is probably not prolactinoma

Lewandowski KC et al. Coexistence of macroprolactinaemia and hyperprolactinaemia in women with oligo-/amenorrhoea is associated with high risk of pituitary adenomas. Gynecol Endocrinol. 2014 May;30(5):385-7.
Kasum M et al. Laboratory and clinical significance of macroprolactinemia in women with hyperprolactinemia. Taiwan J Obstet Gynecol. 2017 Dec;56(6):719-724.
Williams textbook of endocrinology 14th edition

Management of Prolactinoma



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Dopamine Agonist Treatment in Prolactinomas

- Bromocriptine
  - Starting dose: 1.25 mg/day
  - Dose range: 2.5-15 mg/day
    - May increase the dosage up to 30 mg/day
- Cabergoline
  - Starting dose: 0.25 mg/week
  - Dose range: 0.25-3 mg/week
    - May increase the dosage up to 12 mg/week

Thorner MO et al. Rapid regression of pituitary prolactinomas during bromocriptine treatment. *Journal of Clinical Endocrinology and Metabolism* 1980
Samperi I, Lithgow K, Karavitaki N. Hyperprolactinaemia. J Clin Med. 2019 Dec 13;8(12):2203.
Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA; Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Feb;96(2):273-88.

Side Effects of Dopamine Agonists

- Nausea occurs in up to 50% of patients
- Nasal stuffiness
- Depression
- Digital vasospasm
- Psychosis or exacerbation of preexisting psychosis
- Hypersexuality and disordered impulse control

Other Concerns After Treatment

- CSF rhinorrhea
  - It occurred in up to 9% of patients with macroadenomas
  - It could occur spontaneously or after dopamine agonist treatment
  - Surgery is required

- Pituitary apoplexy
  - Rates of apoplexy in macroprolactinomas treated with dopamine agonists were not significantly higher than in untreated macroprolactinomas.

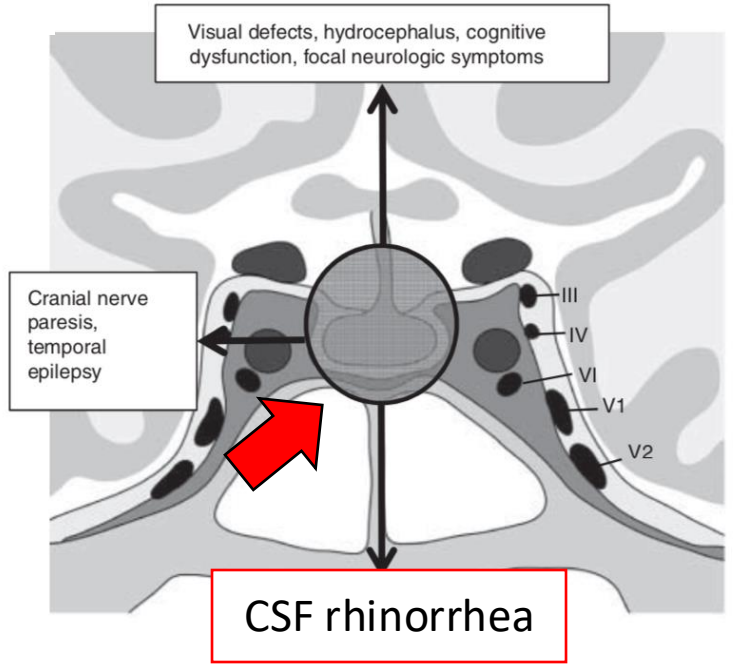

Image from Therapy of endocrine disease: the challenges in managing giant prolactinomas. Eur J Endocrinol. 2014

Honegger J, Nasi-Kordhishti I, Aboutaha N, Giese S. Surgery for prolactinomas: a better choice? Pituitary. 2020 Feb;23(1):45-51.

Lam G, Mehta V, Zada G. Spontaneous and medically induced cerebrospinal fluid leakage in the setting of pituitary adenomas: r eview of the literature. Neurosurg Focus. 2012 Jun;32(6):E2

Carija R, Vucina D. Frequency of pituitary tumor apoplexy during treatment of prolactinomas with dopamine ago- nists: a systematic review. *CNS Neurol Disord Drug Targets*. 2012;11:1012–1014

Briet C, Salenave S, Bonneville JF, Laws ER, Chanson P. Pituitary Apoplexy. Endocr Rev. 2015 Dec;36(6):622-45.

Cardiac Valvulopathy & Dopamine Agonist

- If long-term treatment with ***high-dose (>2.0 mg/wk) cabergoline*** is anticipated, the Pituitary Society Guideline 2023 suggested performing baseline echocardiography to detect any pre-existing valve alterations.
  - Baseline evaluation can be performed before starting cabergoline therapy or during the first few months of treatment (weak recommendation).

Petersenn S et al. Nat Rev Endocrinol 2023. PMID: 37670148.

Dopamine Agonist Treatment in Prolactinomas

	Bromocriptine[a]	Cabergoline[a]
PRL normalized (range, 40-100%)		
• Macroadenomas	70	80
• Microadenomas	65	70
Menses resumed (range, 40-100%)		
• Macroadenomas	70	80
• Microadenomas	85	80
Tumor shrinkage (range, 20-100%)		
• None	20	20
• Up to 50%	40	55
• 50% or more	40	25
Visual field improvement (range, 33-100%)	90	70
Drug intolerance	15	5

[a]Values = % of patients

Webster J, Piscitelli G, Polli A, Ferrari CI, Ismail I, Scanlon MF. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. N Engl J Med. 1994 Oct 6;331(14):904-9.
Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA; Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Feb;96(2):273-88.
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Prolactinoma: Monitoring of Treatment

Periodic PRL measurement

- ***1 month*** after dopamine agonist treatment

Pituitary MRI

- After dopamine agonist treatment → ***repeat MRI in 1 year (3 months if macroprolactinoma)***
- If PRL continue to rise while on medication
- If new symptoms occur e.g. headache, visual disturbances

Visual field

- In patients with macroadenomas at risk of impinging the optic chiasm

Assessment and management of comorbidities

- BMD in patients with >6 months hypogonadism or with other risk factors for osteoporosis
- Pituitary trophic hormone reserve – hormonal deficiency, particularly in those with macroadenoma
- IGF1 – evaluate if there is a cosecretion of GH
- MEN1 germline mutation screening – consider in patients with a family history of pituitary adenomas & in patients <30 years with pituitary macroadenoma

Melmed S et al. J Clin Endocrinol Metab 2011. PMID: 21296991.
Petersenn S et al. Nat Rev Endocrinol 2023. PMID: 37670148.

When to Discontinue Medication

- During treatment, dopamine agonists can be tapered and discontinued in
  - Favorable predictors of successful withdrawal include ***low maintenance doses of cabergoline***, treatment duration ***>2 years*** and ***substantial adenoma size reduction*** (Pituitary Society 2023)
  - Patients who have been on treatment for ***at least 2 years***, with ***no longer PRL elevation*** & ***no visible tumor remnant on MRI*** (Endocrine Society 2011)

- In women with microprolactinomas when;
  - Pregnancy
  - Menopause

Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA; Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Feb;96(2):273-88.
Casanueva FF et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol (Oxf). 2006 Aug;65(2):265-73.

Surgery in Prolactinomas

- Transsphenoidal surgery can be offered to patients with
  - Drug intolerance
  - Dopamine agonist-resistant prolactinoma
  - It can be considered in women with large prolactinomas (that could potentially threaten vision during pregnancy)
  - CSF rhinorrhea

  - Pituitary apoplexy, Mixed GH-prolactin tumor (Pituitary Society 2023)

Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA; Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Feb;96(2):273-88.

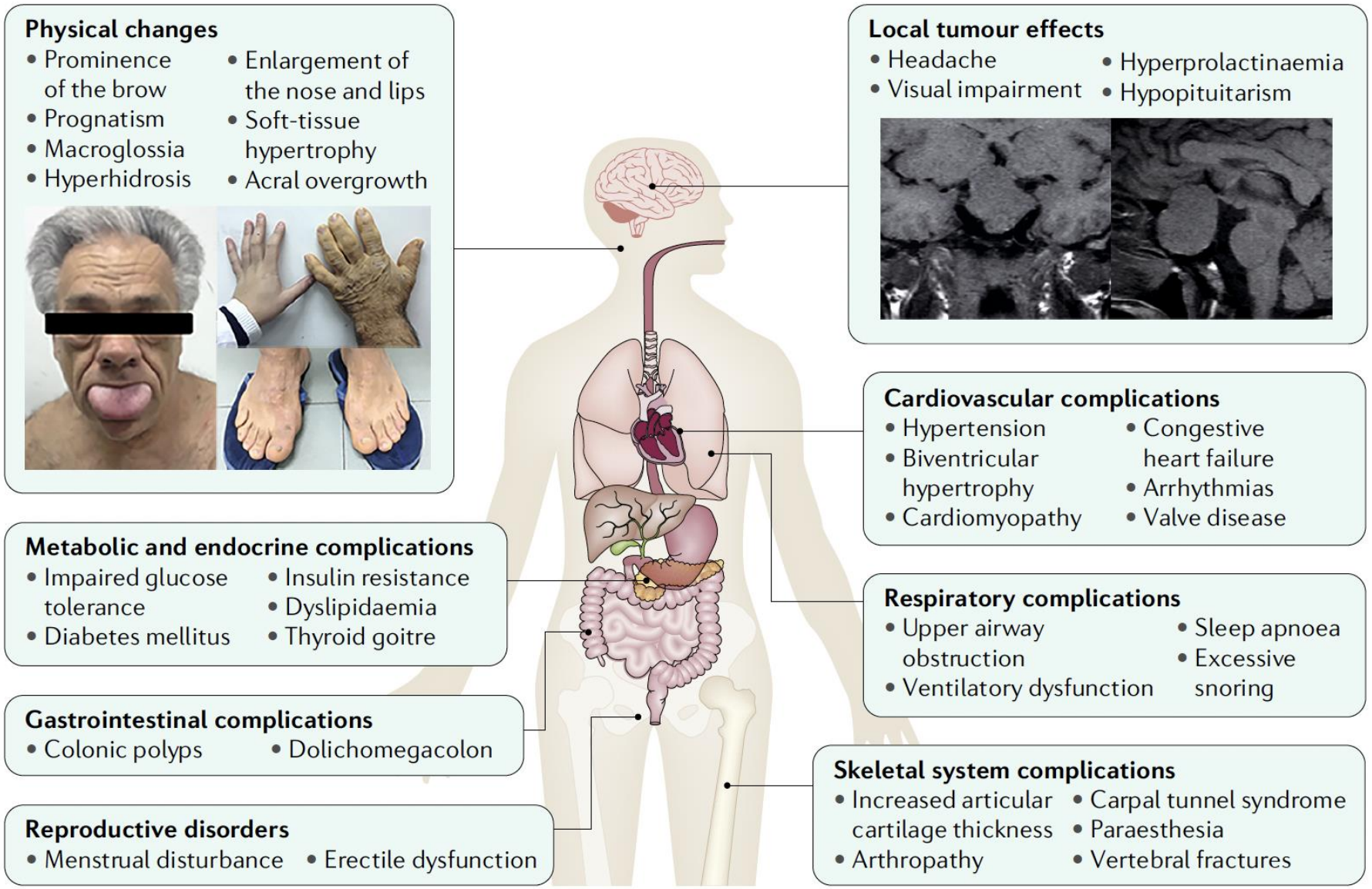
Acromegaly

มือเท้าใหญ่ คางยื่น ฟันไม่สบกัน หน้าเปลี่ยน ลิ้นใหญ่ จมูกใหญ่ นอนกรน ใส่แหวนไม่ได้ รองเท้าเปลี่ยนไซส์ มีติ่งเนื้อที่ลำตัว เสียงเปลี่ยน

เบาหวาน ก้อนที่คอ คอโต

ความดันโลหิตสูง ประวัติ HF

ปวดตามข้อ มีอาการ carpal tunnel syndrome



Colao A et al. Nat Rev Dis Primers 2019. PMID: 30899019.

ขอดูบัตรประชาชน หรือ ID card อื่นๆ!!!

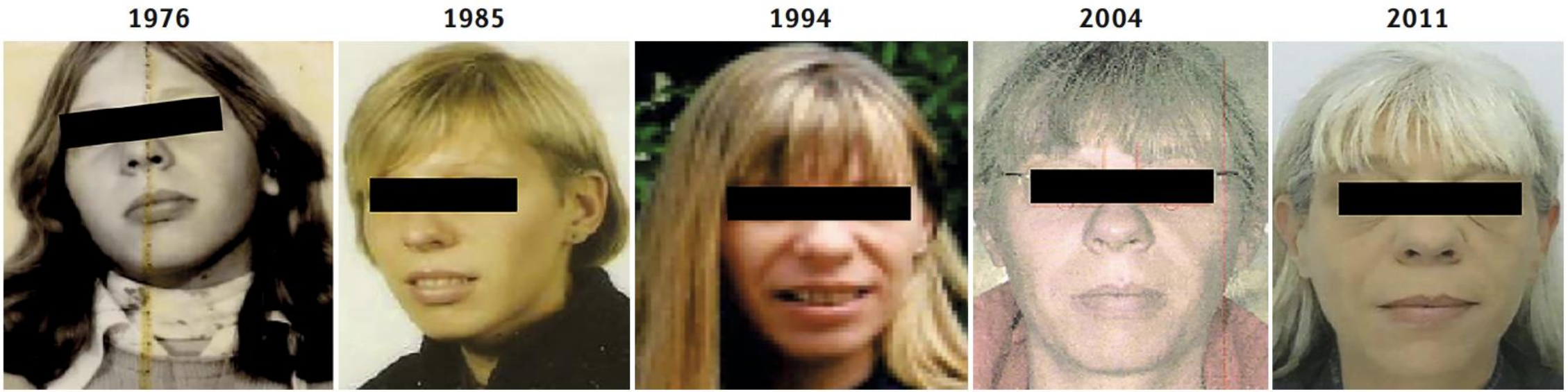
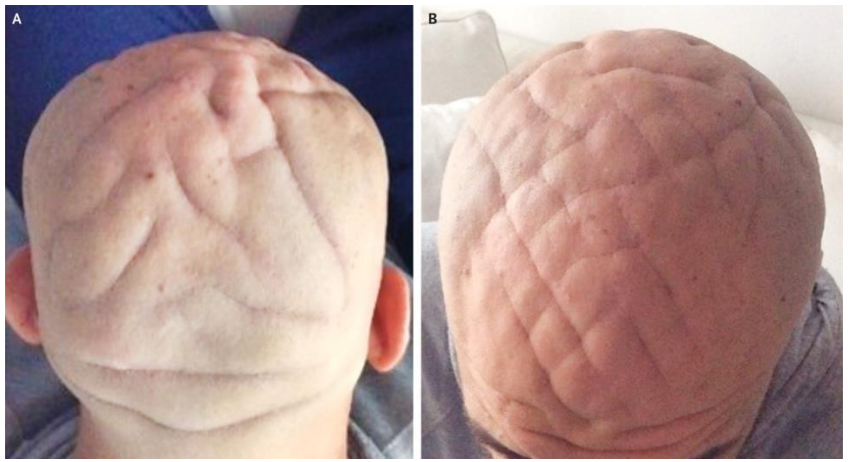


Fig. 5 | **Progressive changes in facial appearance in a patient with acromegaly.** On the basis of an analysis of these photographs (and others that are not shown), as well as the fact that the patient had a ring (purchased in 1988) removed from her finger in 1990, the disease probably began between 1988 and 1990, 22 years before the diagnosis of acromegaly that was made in 2011. Adapted with permission from REF.[78], Elsevier.

Colao A et al. Nat Rev Dis Primers 2019. PMID: 30899019.

Acromegaly: Physical Examination

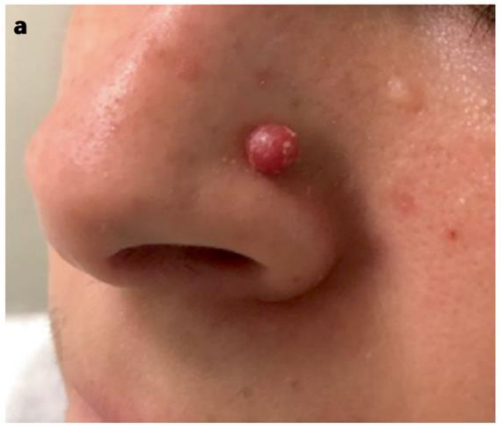
- วัด BP
- Visual field: VF defect, bitemporal hemianopia
- HEENT:
  - Cutis verticis gyrata
  - Coarse face, thick lip, big nose, macroglossia
  - Prominent supraorbital ridge, prognathism, malocclusion
  - Thyroid gland: enlargement, nodules
- Abdomen: hepatosplenomegaly
- Cardiovascular: heave/thrill, murmur, gallop
- Musculoskeletal: Spade-like hands and feet, Tinel/Phalen's test
- Skin: acanthosis nigricans, skin tag, oily skin
- Others e.g., skin signs in MEN1 - lipoma, facial angiofibroma, collagenoma



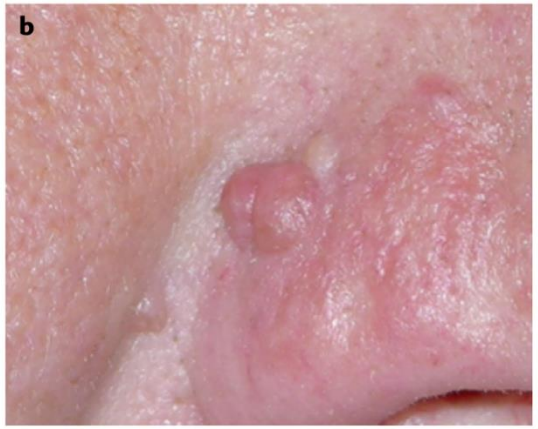
Cutis verticis gyrata

Image from Parolin M, Dassie F. N Engl J Med 2019. PMID: 31042829.

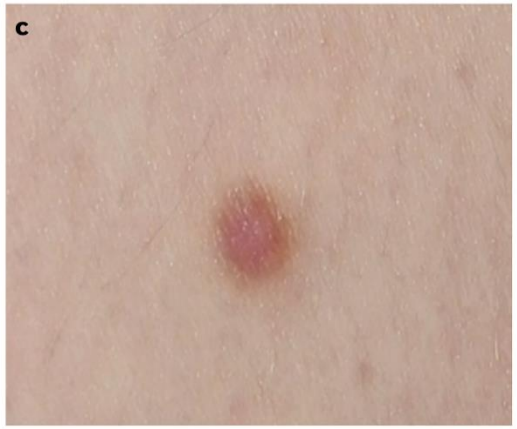
Skin Signs in MEN1



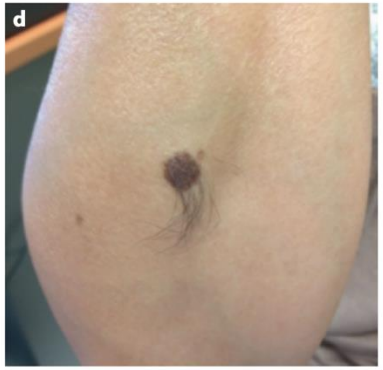
Facial angiofibroma

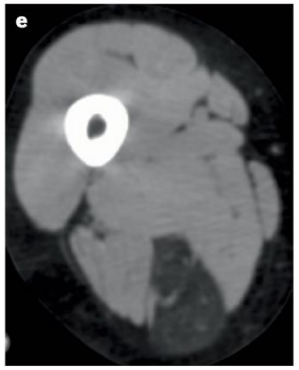


Collagenoma



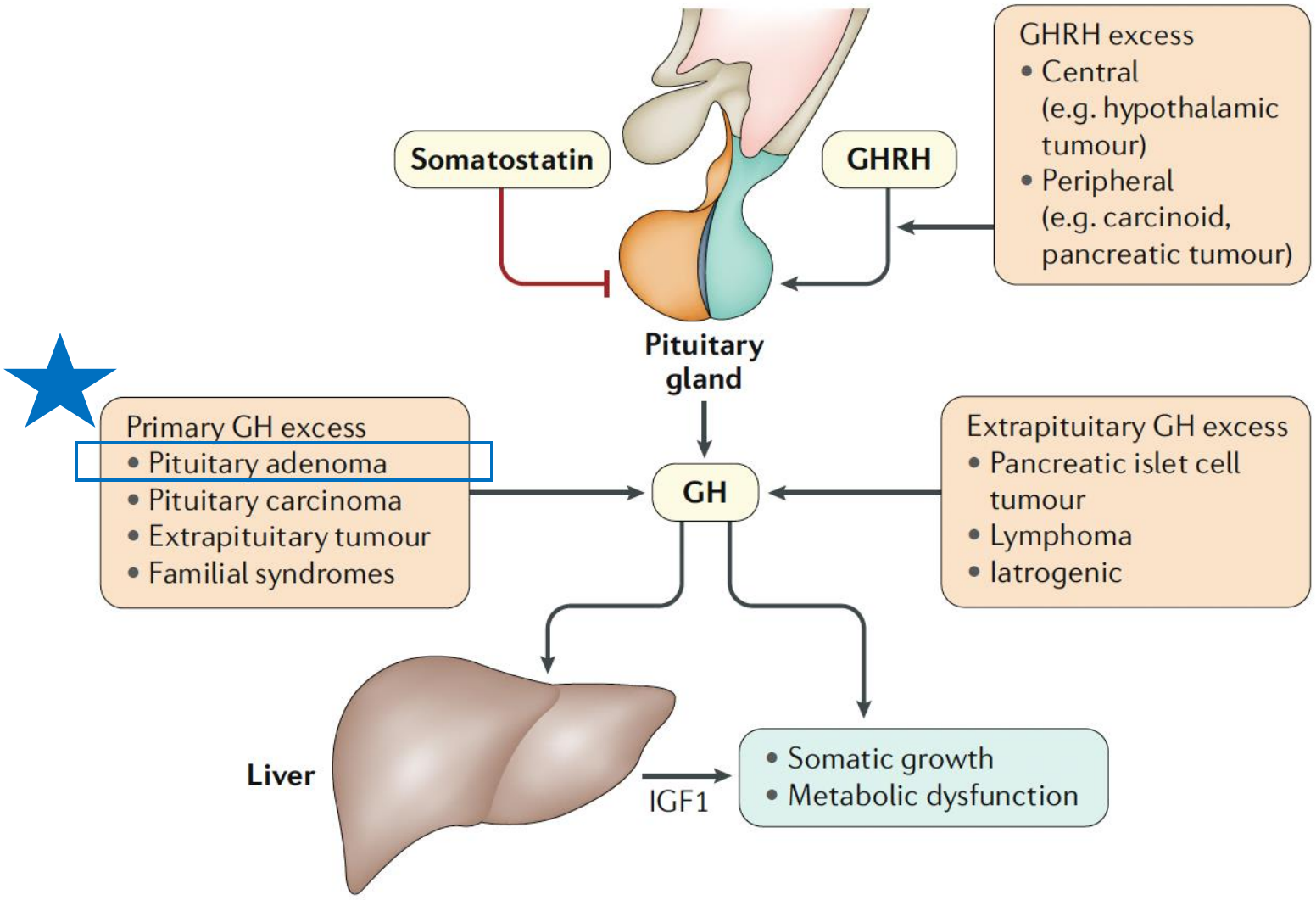
Histiocytofibroma





Lipoma

Etiology of Acromegaly



Colao A et al. Nat Rev Dis Primers 2019. PMID: 30899019.

Evolution of Criteria for Acromegaly Diagnosis

	Diagnosis	Therapeutic efficacy target
1st Acromegaly consensus [3]	IGF-I elevated for age and sex Confirm with random GH ≥ 0.4 µg/L *or* IGF-I elevated for age and sex Confirm with GH > 1 µg/L during OGTT	IGF-I normalized for age and sex GH < 1 µg/L during OGTT
7th Acromegaly consensus [4]	IGF-I elevated for age and sex *and* Random GH elevated	Random GH < 1 µg/L GH < 0.4 µg/L during OGTT
Endocrine society guidelines [5]	IGF-I elevated for age Confirm with GH > 1 µg/L during OGTT	IGF-I normalized for age Random GH < 1 µg/L
14th Acromegaly consensus (this publication)	IGF-I > 1.3 × ULN for age *and* Characteristic clinical signs of disease For equivocal results, IGF-I measurements can be repeated, and OGTT might additionally be useful	IGF-I normalized for age

GH growth hormone; *IGF-I* insulin-like growth factor I; *OGTT* oral glucose tolerance test; *ULN* upper limit of normal

For 75 gm OGTT – เจาะเลือดที่ 0, 60, 120 min

Insufficient GH suppression: Nadir GH >0.4 ng/mL (BMI <25 kg/m^2) หรือ >0.2 ng/mL (BMI >25 kg/m^2)

Giustina A et al. Pituitary 2024. PMID: 37923946.

Recommendation for Diagnosis and Treatment of Acromegaly Comorbidities

Assessment	Frequency
Cardiovascular disorders	
Blood pressure measurement	At baseline and every 6 months or upon change of antihypertensive treatment
Echocardiography	Annually, if abnormal
Electrocardiogram	Annually, if abnormal
Endocrine and metabolic disorders	
Epworth scale or sleep study	Baseline or before surgery if OSA is suspected
Fasting blood glucose or OGTT	Fasting blood glucose every 6 months, particularly in uncontrolled disease and during SRL therapy; HbA1c every 6 months if diabetes or prediabetes is present
Total testosterone, SHBG, and PRL (males)	Annually; consider testing free testosterone if there are doubts in interpretation of total testosterone
LH, FSH, 17β-estradiol, and PRL (females)	Annually, in premenopausal females with menstrual dysfunction and when pregnancy is desired
Serum free T4	Annually
Serum 8–9 AM cortisol	If central adrenal insufficiency is suspected; cosyntropin stimulation test if serum cortisol is low
Musculoskeletal disorders	
DXA	Every 2 years particularly if osteopenia/osteoporosis is present
Vertebral morphometry on thoracic x-ray, thoracic and lumbar spine x-ray	Annually, particularly if history of vertebral fracture, decrease in BMD, kyphosis, symptoms of vertebral fracture, untreated hypogonadism, and no biochemical control of acromegaly
Cancer	
Colonoscopy	Every 10 years; more frequently if IGF-I remains persistently elevated or if abnormal colonoscopy or family history of colon cancer
Quality of life	
AcroQoL	Annually

Abbreviations: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; OGTT, oral glucose tolerance test; OSA, obstructive sleep apnea; PRL, prolactin; SHBG, sex hormone binding globulin; SRL, somatostatin receptor ligand.

- Current evidence does not support routine screening for thyroid cancer at acromegaly diagnosis.
- Thyroid ultrasound and careful evaluation is recommended in those with palpable thyroid nodules and other risk factors for thyroid cancer, consistent with guideline recommendations for the general population.

Giustina A et al. J Clin Endocrinol Metab 2020. PMID: 31606735.

Acromegaly: Treatment

- **Specific:** Transsphenoidal surgery with tumor removal
- **Supportive:** Treatment of comorbidities, hormonal supplement (in patients with pituitary hormone deficiency)

Mutations in Acromegaly and Gigantism Syndromes

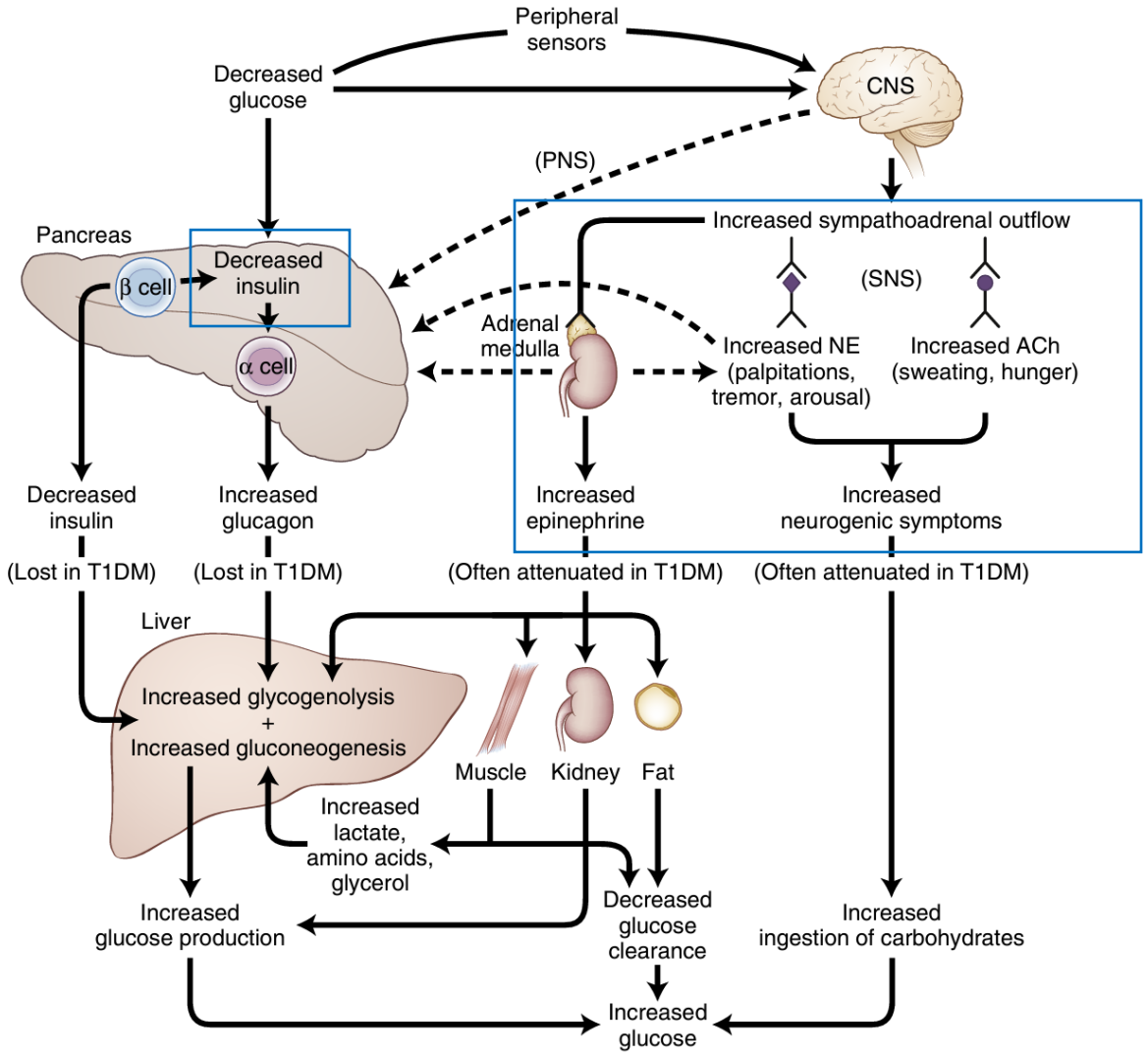
Syndrome	Affected gene	Function	Chromosomal locus	Acromegaly penetrance[a] (%)	Main clinical characteristics
Carney complex	*PRKAR1A*	Tumour suppressor	17q24.2	15	Skin pigmentation; cardiac and cutaneous myxomas; thyroid, testis and adrenal tumours; GH-cell hyperplasia or pituitary adenoma
Familial isolated pituitary adenomas	*AIP*	Tumour suppressor	11q13.2	30	Young familial invasive GH-secreting pituitary adenomas, often resistant to therapy
XLAG	*GPR101*	Oncogene	Xq26.3	100	XLAG due to somatotroph cell hyperplasia or pituitary adenoma
McCune–Albright	*GNAS1*[b]	Oncogene	20q13.32	20	Polyostotic fibrous dysplasia, café-au-lait spots and precocious puberty with GH and/or PRL excess
MEN 1	*MEN1*	Tumour suppressor	11q13.1	10	Pancreatic, pituitary and parathyroid gland tumours
MEN 4	*CDKN1B*	Tumour suppressor	12q13.1	Unknown	MEN-1-like, usually with GH-secreting pituitary adenomas
SDH complex deficiency syndrome	*SDHA*, *SDHB*, *SDHC* and *SDHD*	Tumour suppressor	5p15.33 (*SDHA*), 1p36.13 (*SDHB*), 1q23.3 (*SDHC*) and 11q23.1 (*SDHD*)	Very rare	Acromegaly with paraganglioma or pheochromocytoma

GH, growth hormone; MEN, multiple endocrine neoplasia; PRL, prolactin; SDH, succinate dehydrogenase; XLAG, X-linked acrogigantism. [a]Penetrance values are estimates because of the rarity of these syndromes. [b]Mutations in *GNAS1* are mosaic post-zygotic mutations. Data are taken from REFS[71,73,177].

Colao A et al. Nat Rev Dis Primers 2019. PMID: 30899019.

Hypoglycemia

Physiologic and Behavioral Defenses Against Hypoglycemia



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Hypoglycemia

- Diabetes
  - หากยาที่ใช้อยู่ ไม่ได้เป็นยาที่ทำให้เกิด hypoglycemia ก็ควร approach สาเหตุตามแบบ non-DM ด้วย
- Non-diabetes

TABLE 38.4 Causes of Hypoglycemia in Adults

Ill or Medicated Individual

Drugs

Insulin or insulin secretagogue
Alcohol
Others (see Table 38.8)

Critical Illnesses

Hepatic, renal, or cardiac failure
Sepsis
Inanition

Hormonal Deficiency

Cortisol
Glucagon and epinephrine (in insulin-deficient diabetes mellitus)

Non–Islet Cell Tumor

Seemingly Well Individual

Endogenous Hyperinsulinism

Insulinoma
Functional beta-cell disorders (nesidioblastosis)
Noninsulinoma pancreatogenous hypoglycemia
Post–gastric bypass hypoglycemia
Autoimmune hypoglycemia
  Antibody to insulin
  Antibody to insulin receptor
Insulin secretagogue
Other

Accidental, Surreptitious, or Malicious Hypoglycemia

From Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2009;94:709–728, used with permission of The Endocrine Society.

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TABLE 38.9 Patterns of Findings During Fasting or After a Mixed Meal in Normal Individuals[a] and in Individuals With Hyperinsulinemic (or IGF-Mediated) Hypoglycemia or Hypoglycemia Caused by Other Mechanisms

Symptoms, Signs, or Both	Glucose (mg/dL)	Insulin (μU/mL)	C-Peptide (nmol/L)	Proinsulin (pmol/L)	β-Hydroxybutyrate (mmol/L)	Glucose Increase After Glucagon (mg/dL)	Circulating Oral Hypoglycemic Agent	Antibody to Insulin	Diagnostic Interpretation
No	<55	<3	<0.2	<5	>2.7	<25	No	No	Normal
Yes	<55	≫3	<0.2	<5	≤2.7	>25	No	Neg (Pos)	Exogenous insulin
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	No	Neg	Insulinoma, NIPHS, PGBH
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	Yes	Neg	Oral hypoglycemic agent
Yes	<55	≫3	≫0.2[b]	≫5[b]	≤2.7	>25	No	Pos	Insulin autoimmune
Yes	<55	<3	<0.2	<5	≤2.7	>25	No	Neg	IGF[c]
Yes	<55	<3	<0.2	<5	>2.7	<25	No	Neg	Not insulin- or IGF mediated

[a]Normal individuals are those with no symptoms or signs despite relatively low plasma glucose concentrations (i.e., those in whom Whipple triad is not documented).

[b]Concentrations of free C-peptide and proinsulin are low.

[c]Increased pro-IGF2, free IGF2, and IGF2/IGF1 ratio.

IGF, Insulin-like growth factor; *NIPHS,* noninsulinoma pancreatogenous hypoglycemia; *PGBH,* post–gastric bypass hypoglycemia.

From Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2009;94:709–728, used with permission of the Endocrine Society. Data from Service[152] and Placzkowski and associates.[193] See discussion of Guettier and associates[196] for independent data.

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Thank you

Questions are welcome

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