Hypothalamic and Pituitary Disorders

Part 4

By Dr. Joseph Khatchadourian as of March 14, 2020

(Lecture for Week 4 for Publishing in SPU Website)

Pituitary Hormone Excess

Pituitary Adenomas

1) Lactotroph adenomas (prolactinomas) ≈25% of pituitary tumors
2) Somatotroph adenomas, GH-producing (acromegaly or giagantism), ≈15%
3) Thyrotroph adenomas, TSH-producing, <1%
4) Gonadotroph adenomas, ≈10%

Somatotroph (GH-Producing) Adenoma Causing Acromegaly or Gigantism

- GH exerts much of its growth-promoting effects by stimulating the release of IGF-I from the liver and other tissues

Somatotroph (GH-Producing) Adenoma Causing Acromegaly or Gigantism

- Most are macroadenomas
- These tumors may be locally invasive, particularly into the cavernous sinus

Somatotroph (GH-Producing) Adenoma Causing Acromegaly or Gigantism

- It is usually sporadic but may rarely be familial, and it may be associated with MEN 1 or 4, McCune-Albright Syndrome, and Carney Complex

McCune-Albright Syndrome (MAS)

- **Mutation:** Activating mutation of the *GNAS1* gene (G protein α-stimulating subunit 'Gsα')

- **Features:** characterized by the triad of:
  1) Polyostotic fibrous dysplasia (fractures are common; may be associated with hypophosphatemic rickets)
  2) Café-au-lait skin pigmentation
  3) Hyperfunction of an endocrine system: > > > >

McCune-Albright Syndrome (MAS)

3) : > > > >

- Peripheral precocious puberty
- Somatotrope tumors
- Thyrotoxicosis (may be associated with a multinodular goiter)
- Cushing syndrome (due to adrenal tumors)

Carney Complex (CNC)

- **Mutation:** A subset is due to mutations of the protein kinase A (PKA) regulatory subunit 1 α (R1α) (PPKAR1A) gene (AD)

- **Features:** characterized by:
  - Myxomas (cardiac, skin , and/or breast)
  - Lentigines and/or pigmented nevi
  - Endocrine overactive tumors (adrenal, pituitary, thyroid, testicular, and ovary)

Acromegaly & Gigantism

- Acromegaly is caused nearly always by a pituitary adenoma, <1% by malignant pituitary tumors, very occasionally by *ectopic* GH (tumors of pancreatic, ovarian, lung, or hematopoietic origin) or GHRH secretion (chest or abdominal carcinoid tumors), and by hypothalamic tumors that secrete excessive GHRH

Acromegaly & Gigantism

- Acromegaly can be drug-induced (abuse by athletes, body builders and patients seeking “the fountain of youth”

Acromegaly & Gigantism

- Acromegaly is insidious with a long lag time between disease onset and diagnosis (avg. 10 years)

Acromegaly & Gigantism:

Clinical Findings

Acromegaly & Gigantism: Clinical Findings

- Tall stature & gigantism if excess GH occurs before closure of epiphyses
- If afterward, acromegaly develops
- If hypersecretion starts in adolescence and persists into adult life, then the two conditions may be combined

Acromegaly & Gigantism: Clinical Findings

- The term ‘acromegaly’ seriously understates the manifestations

Acromegaly & Gigantism: Clinical Findings

- Coarse facial features
- Enlarged supraorbital ridges with large fontal sinuses
- Increased hat size
- Large fleshy nose
- Large lips
- Prominent lower jaw (prognathism) and malocclusion
- Widened tooth spacing

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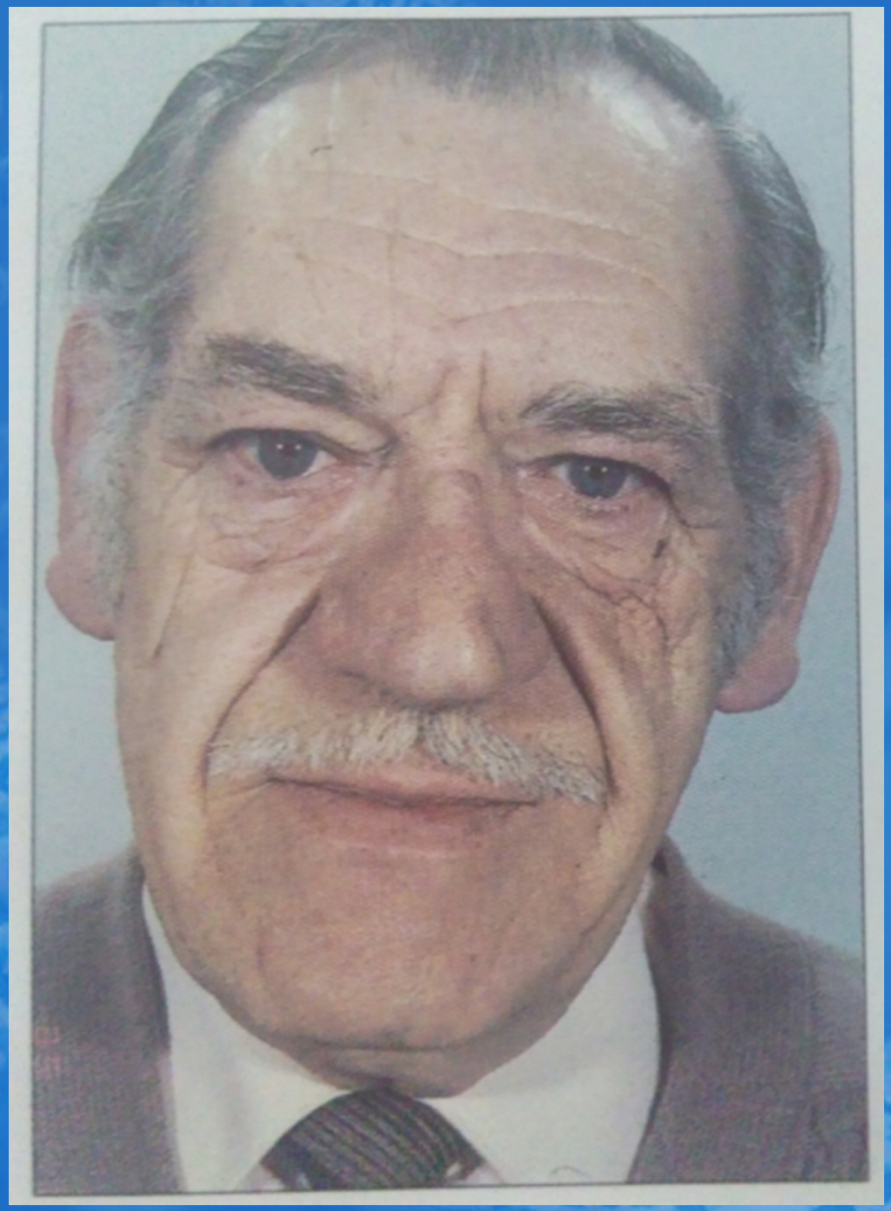

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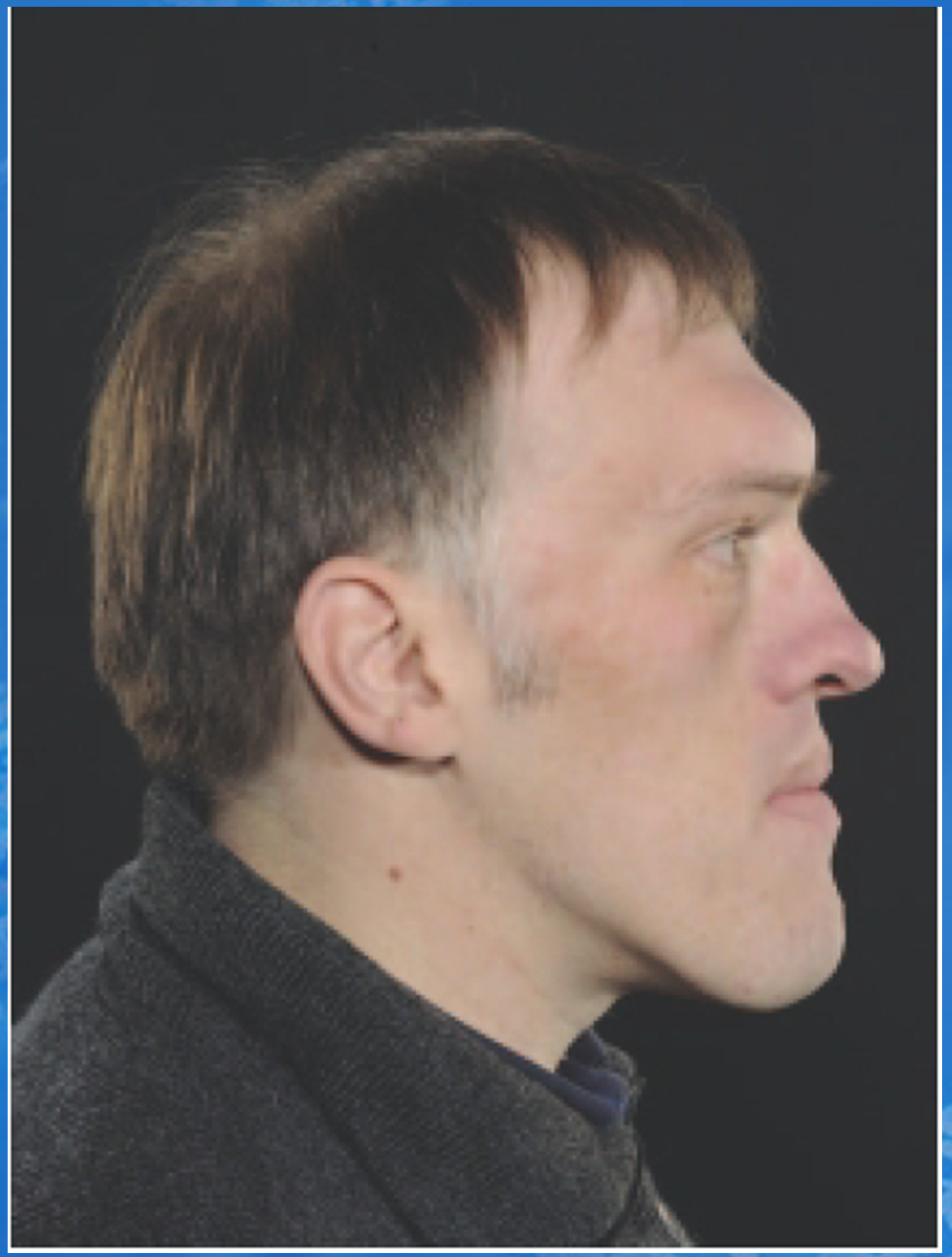

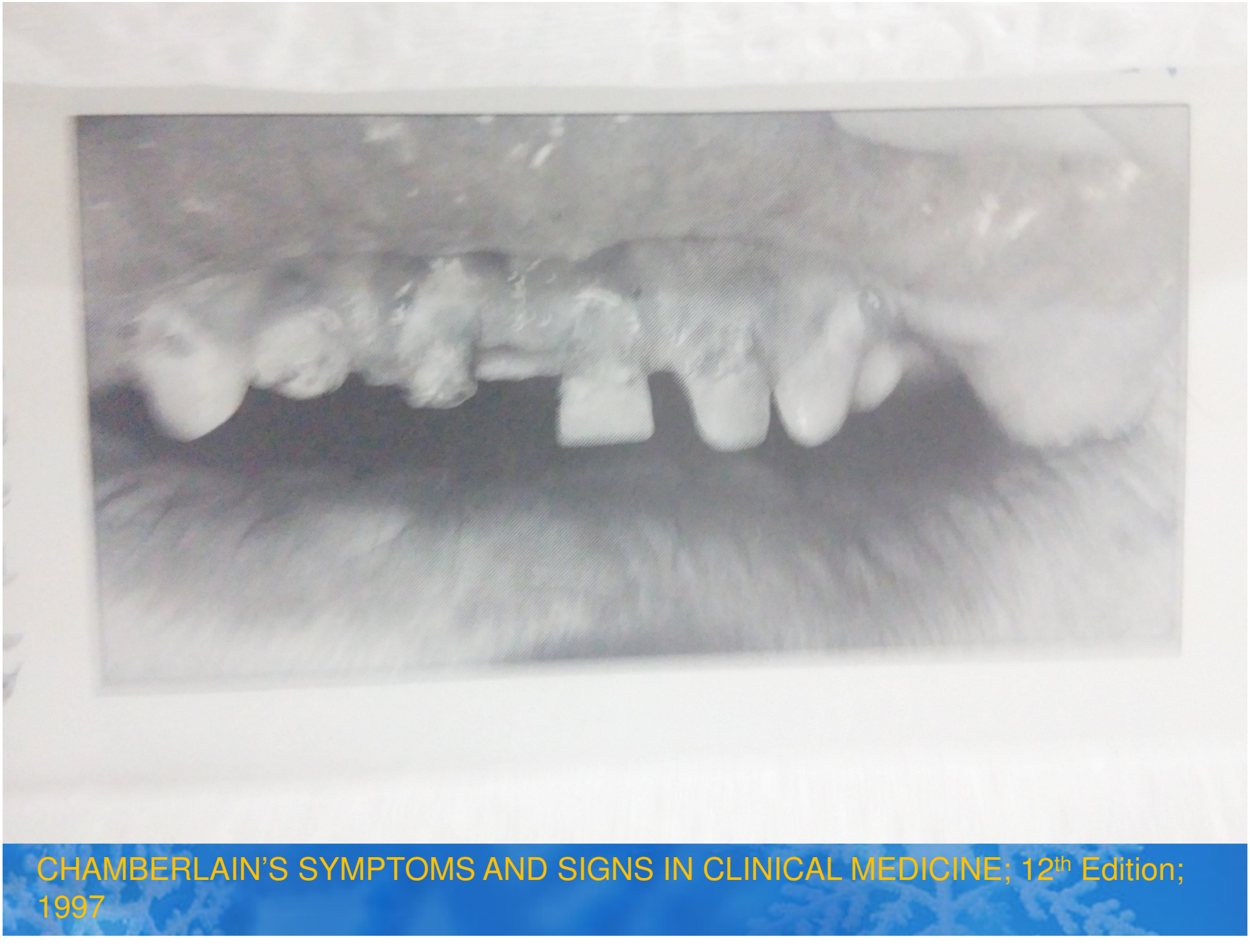

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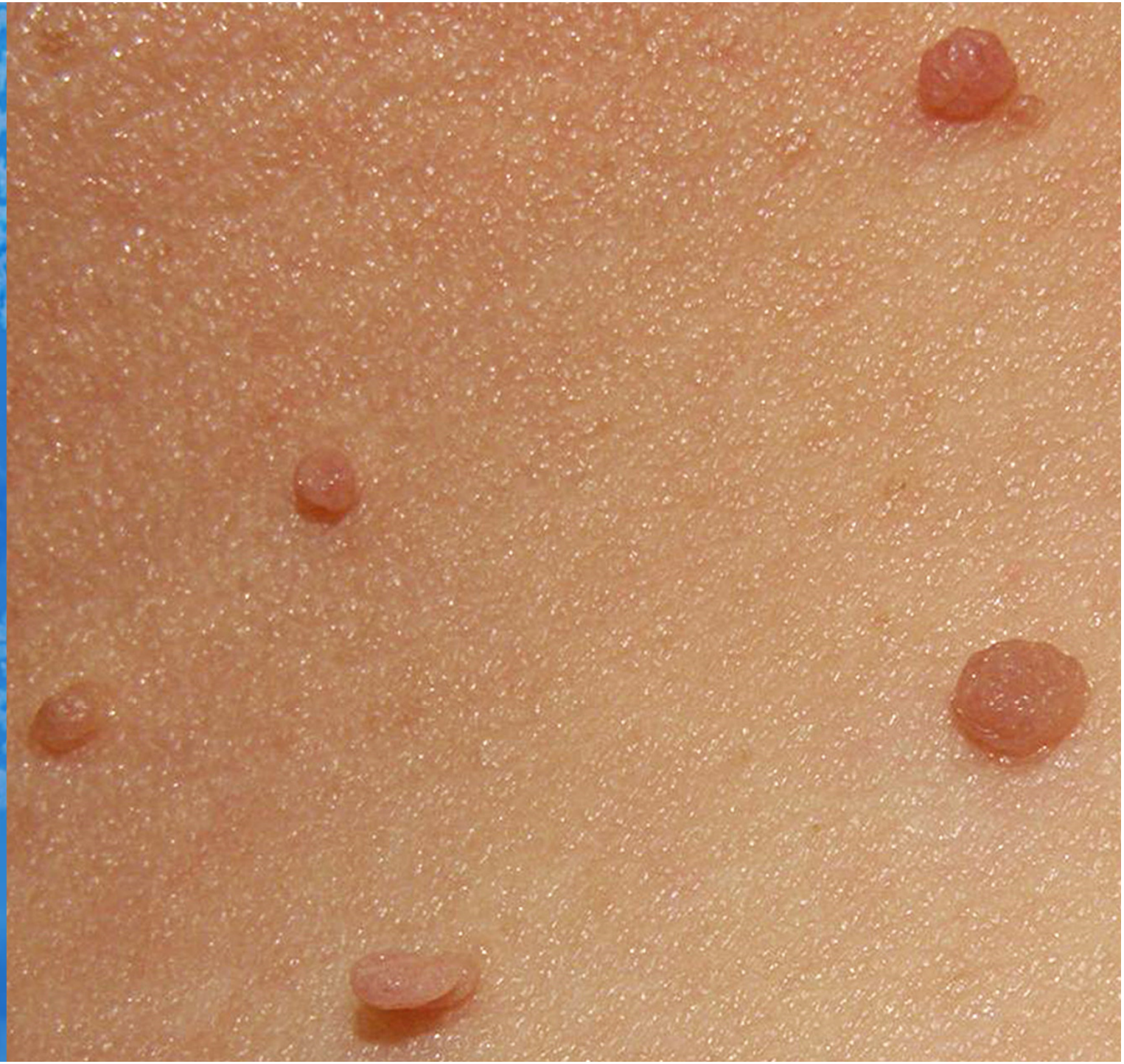
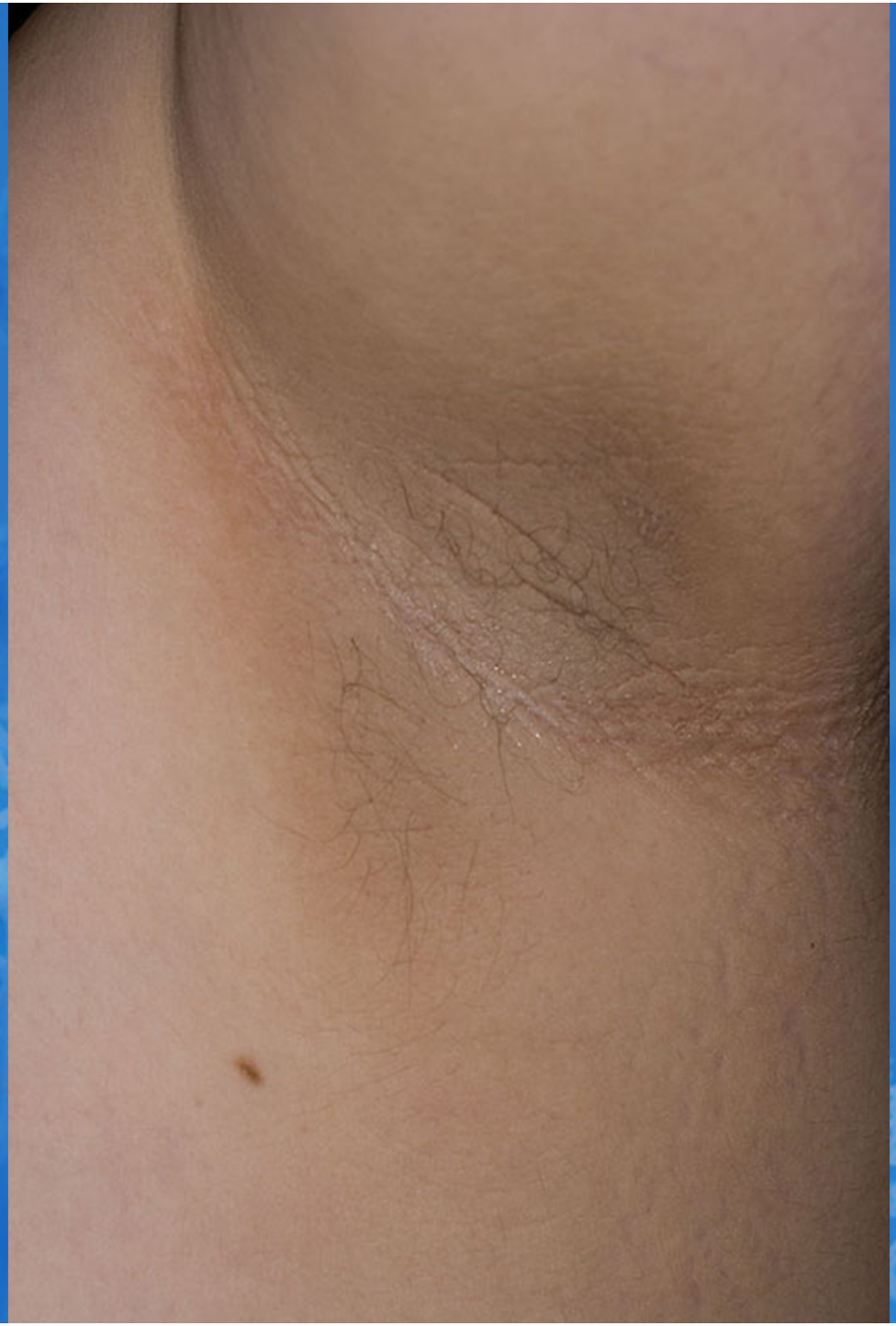
Acromegaly & Gigantism: Clinical Findings

- Macroglossia, hypertrophy of pharyngeal and laryngeal tissue ~ deep coarse voice, Obstructive Sleep Apnea (OSA)
- Central Sleep Apnea can occur as well
- Skin: thick, oily, sweaty, acne, tags, acanthosis nigricans

Skin Tags





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Acromegaly & Gigantism: Clinical Findings

- Enlarged hands (increased glove size), and a doughy moist handshake is characteristic, widened fingers (increased ring size), carpal tunnel syndrome
- Enlarged feet (increased shoe size), increased heel pad thickness

Identical twin, one with acromegaly

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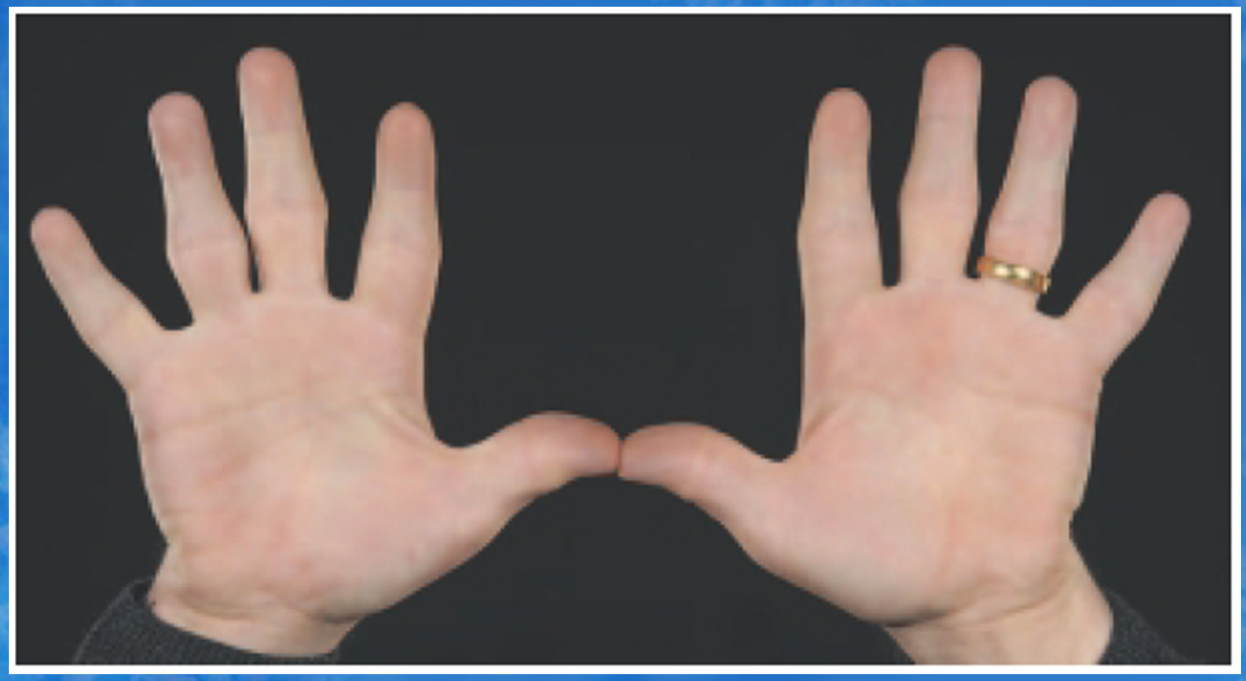

Acromegaly & Gigantism: Clinical Findings

- Generalized visceromegaly occurs, including thyroid gland enlargement (goiter) and hepatomegaly
- CVD (2-3 x↑): HTN, cardiomegaly, cardiomyopathy with arrhythmias, LVH, ↓ diastolic function
- Weight gain (↑ muscle and bone mass)

Acromegaly & Gigantism: Clinical Findings

- Arthropathy
- Proximal myopathy
- Insulin resistance, glucose intolerance, diabetes mellitus
- Colon polyps and colonic caner

Acromegaly & Gigantism: Clinical Findings

- Pressure effects of a large pituitary tumor including headache and hypopituitarism

- Hypogonadism from hypopituitarism or an associated ↑ PRL co-secretion (plurihormonal adenoma)

Acromegaly & Gigantism: Clinical Findings

- Overall mortality is increased about threefold and is due primarily to cardiovascular and cerebrovascular disorders and respiratory disease

- Unless GH levels are controlled, survival is reduced by an average of 10 years compared with an age-matched control population

Acromegaly & Gigantism: Clinical Findings

- For screening purposes, a normal for age random serum IGF-1 rules it out

- Due to the pulsatility of GH secretion, measurement of a single random GH level is not useful for the diagnosis or exclusion of acromegaly and does not correlate with disease severity

Acromegaly & Gigantism: Clinical Findings

- For diagnosis confirmation, a 2-hr glucose suppression test should be performed as follows:
  - Fasting (8-hr) Glucose & GH
  - Consuming 75 g oral glucose
  - GH & Glucose levels every 30 min for 2 hours

Acromegaly & Gigantism: Clinical Findings

- If GH falls to <0.4 mcg/L during the test, acromegaly is excluded (<0.05 if ultrasensitive GH assays are used)

- The initial imaging study should be a pituitary MRI without & with contrast to evaluate for pituitary adenoma

Acromegaly & Gigantism: Management: TS Pituitary Surgery

- It's the treatment of choice (first line of treatment)
- More successful with smaller tumor sizes (<2 cm) than larger sizes

Acromegaly & Gigantism: Management: Medical Therapy

- For patients who do not have remission after surgery
- Options are one or any combination of:
  - Somatostatin analogs (octreotide, lanreotide, or pasireotide) (sc)
  - DAs (eg, cabergoline) (po)
  - Pegvisomant (GH receptor antagonist that blocks IGF-1 production) (sc)

Acromegaly & Gigantism: Management: Medical Therapy

- Somatostatin analogs can also be used as primary therapy for acromegaly either as an alternative or in advance of surgery, given evidence that they can induce modest tumor shrinkage in some patients

Acromegaly & Gigantism: Management: Radiotherapy

- For patients who haven't had a complete remission with surgery or medical Rx
- GH levels fall slowly (over many years) and there is a risk of hypopituitarism
- Shouldn't be used for pituitary tumors with suprasellar extension due to the risk of damaging the optic chiasm

Acromegaly & Gigantism: Management

- Colonoscopy is recommended to all patients

Pituitary Hormone Excess

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Thyrotroph (TSH-Producing) Adenoma

- They're usually large macroadenomas

- Presentation:
  - Pressure effects including hypopituitarism
  - Hyperthyroidism and goiter
  - GH may be co-secreted=> acromegaly
  - PRL may be co-secreted=>↑ PRL

Thyrotroph (TSH-Producing) Adenoma

- ↑ FT4, ↑FT3, ↑ alpha subunit (ASU) with non-suppressed TSH (↑ or inappropriately normal), and ↑ASU/TSH molar ratio

- Pituitary tumor of ≥6 mm seen in MRI

Thyrotroph (TSH-Producing) Adenoma

- **Treatment:**
  - If a surgical candidate => Surgery (TSS)
  - If not, somatostatin analog (SSA) Rx
  - ATD (Anti-Thyroid Drug) & β-blocker
  - May require radiotherapy (failed TSS)

Thyrotroph (TSH-Producing) Adenoma

- **Treatment:**
  - If tumor <6 mm: the differential diagnosis then can be Resistance to Thyroid Hormone (RTH) with non-functioning incidentaloma => consider empiric SSA therapeutic trial *versus* alternate imaging (i.e., octreotide scan)

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Gonadotroph Adenoma

- Results in ↑ FSH, and rarely ↑ LH
- It's usually macroadenoma
- Presentation:
  - Pressure effects including hypopituitarism
  - If FSH/LH produced => hypogonadism (gonadal down-regulation)
- Treatment: TSS, and if failed, radiotherapy

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Pituitary Adenomas

5) **Corticotroph adenomas**, ACTH-producing (Cushing disease), ≈15%

6) **Plurihormonal adenomas**, ≈15% , produce >1 type of hormone (any mixture, such as GH/PRL, TSH/GH, TSH/PRL)

7) **Null cell adenomas**, ≈20%, <u>no</u> hormone excess

Pituitary Hormone Excess

Pituitary Adenomas

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Pituitary Hormone Excess

Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

SIADH

- Under normal circumstances, hypovolemia and hyperosmolality stimulate ADH secretion
- Without these physiologic cues, ADH release is inappropriate

SIADH

- Normal regulation of ADH release occurs from both the central nervous system (CNS) and the chest via neural input and baroreceptors

- So CNS disorders (structural or psychiatric) and pulmonary lesions (infectious or mechanical) can cause SIADH

SIADH

- **Some carcinomas**, especially small cell lung carcinoma, can autonomously secrete ADH
- **Some medications** can cause SIADH by increasing ADH production or its action
- **Other causes** (such as pregnancy, pain, stress, postoperative, and acute intermittent porphyria) can also cause SIADH

SIADH

- Examples of **drugs that can cause SIADH by increasing ADH *production***:
  - Antidepressants: tricyclics 'TCAs', SSRIs, monoamine oxidase inhibitors (MAOIs)
  - Antipsychotics (typicals such as phenothiazines more often than atypicals)
  - Antineoplastics: cyclophosphamide, vincristine
  - Carbamazepine

SIADH

- Examples of **drugs that can cause SIADH by increasing ADH *action***:
  - Cyclophosphamide
  - Carbamazepine
  - Amiodarone
  - Chlorpropamide

SIADH

- Of course, ADH analogs (vasopressin, desmopressin, oxytocin) can cause SIADH

- SIADH can sometimes be idiopathic

SIADH

- Symptoms and signs are linked to the **underlying cause**

and/or

- They're secondary to the resulting **hyponatremia** (antidiuresis decreases the volume and increases the concentration of urine, and if not accompanied by a commensurate reduction in fluid intake or an increase in insensible loss, the reduction in urine output results in excess water retention which expands and dilutes body fluids)

SIADH

- SIADH is a clinical diagnosis characterized by:
  (1) Euvolemia on physical examination;
  (2) Hyponatremia;
  (3) decreased plasma osmolality (<280 mOsm/kg [280 mmol/kg])
  (4) absence of heart, kidney, or liver disease;
  (5) normal thyroid and adrenal function;
  (6) urine sodium usually >20 mEq/L

SIADH

- In clinical practice, ADH levels are not measured

- Patients with SIADH may have **low blood urea nitrogen (BUN)** (<10 mg/dL) (**urea** ~ <20 mg/dL) and **hypouricemia** (<4 mg/dL), which are not only dilutional but result from increased urea and uric acid clearances in response to the volume-expanded state

SIADH

- Azotemia may reflect volume contraction, ruling out SIADH (which is seen in euvolemic patients as noted)

SIADH

- Treatment is directed to
  - the underlying cause

    and to
  - the hyponatremia

Pituitary Disease

- It is generally manifest as clinical problems associated with one or more of:
  1) Hypopituitarism (pituitary underfunction)
  2) Pressure effects from a large pituitary or para-pituitary lesion
  3) Pituitary hormone excess
  4) **Pituitary hormone resistance**
  5) Pituitary incidentaloma

Pituitary Hormone Resistance

- Nephrogenic Diabetes Insipidus
- Laron Syndrome

Pituitary Hormone Resistance

- Nephrogenic Diabetes Insipidus
- Laron Syndrome

Pituitary Hormone Resistance:
Laron Syndrome

- An autosomal recessive disorder

Pituitary Hormone Resistance: Laron Syndrome

- Mainly caused by mutations in the gene that encodes the GH receptor, resulting in GH-resistance and a severe deficiency in serum IGF-1, resulting in short stature (dwarfism) and characteristic features (prominent forehead, depressed nasal bridge, small mandible, and central obesity; may have hypoglycemic seizures)
- Typically, it is resistant to GH Rx

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Pituitary Incidentaloma

- Patients should undergo clinical & laboratory evaluations for hormone hypersecretion
- If macroadenoma, should also undergo clinical & laboratory evaluations for hypopituitarism
- if abutting the chiasm or the ONs on MRI: Should undergo formal visual field exam
- Should have MRI scan if not done initially to better delineate its nature and extent

Pituitary Incidentaloma

- Surgery Rx:
  - Abutting or compressing the chiasm or optic nerve (ON) on MRI
  - Hypersecreting other than prolactinoma
  - Pituitary apoplexy with visual disturbance
  - Visual abnormalities such as VF defect or ophthalmoplegia

Pituitary Incidentaloma

- Surgery Rx (may consider):
  - Significant tumor growth
  - Hypopituitarism
  - Close to the optic chiasm and a plan to become pregnant
  - Unremitting headache

Pituitary Incidentaloma: Follow-up if no Srx

- **Imaging:**
  - MRI 6 months later if macroadenoma or 1 year later if microadenoma
  - If no growth, MRI q1 year if macro or q1-2 year if micro for the following 3 years, and gradually less frequently thereafter

Pituitary Incidentaloma: Follow-up if no Srx

- **VF testing:**
  - If tumor enlarges to abut or compress the chiasm or ONs on a follow-up MRI

Pituitary Incidentaloma: Follow-up if no Srx

- **Evaluation for hypopituitarism:**
  - Clinical and biochemical, after 6 months and yearly thereafter in macroadenomas, especially if enlarging
  - No need if microadenoma

Pituitary Disease

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Null Cell/Non-Functioning Adenoma

if Microadenoma

- **Risk for growth is low**
- **MRI can be repeated as noted in incidentaloma**
- **Surgery not indicated unless significant growth is demonstrated**

Null Cell/Non-Functioning Adenoma

if Macroadenoma

- And asymptomatic, MRI can be repeated as noted in incidentalomas, and surgery may be deferred unless there is evidence for growth
- And accompanied by pressure effects (optic chiasm compression, cavernous sinus invasion, hypopituitarism), surgery should be performed and radiotherapy considered; 10% respond to bromocriptine w tumor size reduction

Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD)

Nephrogenic SIAD (NSIAD)

- It results from constitutively activating mutations of the V2 receptor gene
- It is familial
- It results in antidiuresis with euvolemic hyponatremia (from the AVP-independent activation of the renal V2 receptors)
- Plasma AVP is appropriately ??? …

Nephrogenic SIAD (NSIAD)

- It results from constitutively activating mutations of the V2 receptor gene
- It is familial
- It results in antidiuresis with euvolemic hyponatremia (from the AVP-independent activation of the renal V2 receptors)
- Plasma AVP is appropriately **suppressed**

Nephrogenic SIAD (NSIAD)

- Depending on the type of the mutation, it may be refractory or responsive to the treatment with a vaptan

The Vaptans

- The Vaptans (such as conivaptan and tolvaptan) are vasopressin V-2 receptor antagonists that block the antidiuretic effect of AVP and thus increasing urine output

The Vaptans

- They are indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia [s-Na <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction], including patients with heart failure, cirrhosis, and SIADH
- They are contraindicated in hypovolemic hyponatremia

Empty Sella

Empty Sella

- A partial or apparently totally empty sella is often an incidental MRI finding
- May be associated with intracranial hypertension
- Patients usually have normal pituitary function (implying that the surrounding rim of pituitary tissue is fully functional)

Empty Sella

- However, hypopituitarism may develop insidiously

- Also, pituitary masses may undergo clinically silent infarction and involution with development of a partial or totally empty sella by CSF filling the dural herniation

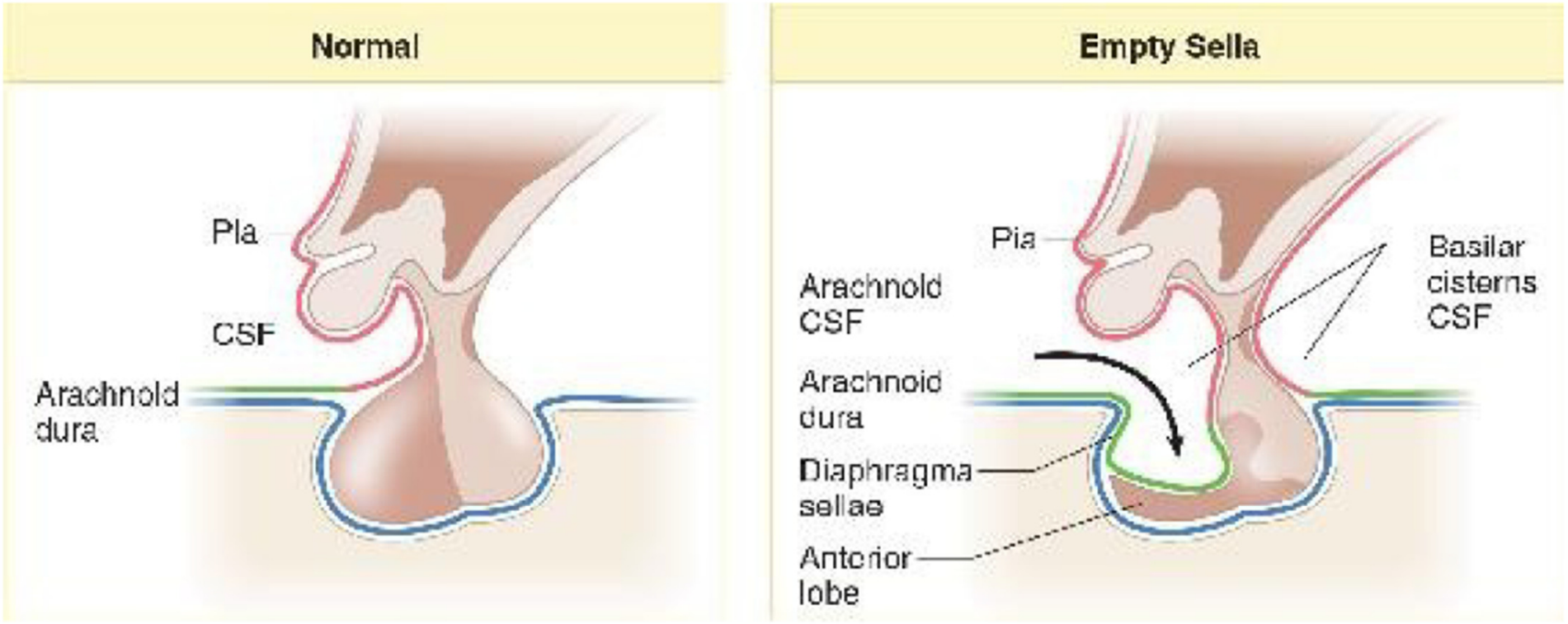

Figure 2-4. Empty Sella Syndrome

Empty Sella

- It can be primary (idiopathic) and is also associated with head trauma, surgery, and radiation therapy

Empty Sella

- Empty sella is in the differential diagnosis of enlarged sella caused by pituitary tumors (no sellar bony erosion in the empty sella)

Empty Sella

- Rarely, small but functional pituitary adenomas may arise within the rim of normal pituitary tissue, and they are not always visible on MRI