Pituitary tumors: clinical and laboratory diagnosis

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- Size of a pea (< 8 mm)
- It weighs about 0.5 gm.
- The pituitary gland occupies a cavity of the sphenoid bone called sella turcica
- Roof is formed by diaphragm sellae
- The stalk of pituitary is attached above to the floor of third ventricle

Potts et al, 2011.

Suprasellar Rathke cleft cysts: clinical presentation and treatment outcomes.
1, Genu of corpus callosum. 2, Splenium of corpus callosum. 3, Neurohypophysis. 4, Antehypophysis.
1. Pituitary gland.
2. Infundibulum.
3. Chiasma.
4. Lateral ventricle.
5. Anterior cerebral artery.
6. Middle cerebral artery.
7. Sphenoidal sinus.
Classification systems used to characterize pituitary adenomas

(a) Hardy classification system
- Noninvasive (enclosed)
  - Grade 0
  - Grade I
- Invasive
  - Grade II
  - Grade III
  - Grade IV

(b) Knosp classification system
- Grade 0
- Grade 1
- Grade 2
- Grade 3
- Grade 4
### Tumors of the pituitary

Table 2: Tumors of the pituitary and sellar regions in the German Registry of Pituitary Tumors, 1996–2005 (N=4122).

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Number (N)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary adenoma</td>
<td>3489</td>
<td>84.6</td>
</tr>
<tr>
<td>Pituitary carcinoma</td>
<td>5</td>
<td>0.12</td>
</tr>
<tr>
<td>Craniopharyngioma, adamantinous</td>
<td>121</td>
<td>2.9</td>
</tr>
<tr>
<td>Craniopharyngioma, papillary</td>
<td>12</td>
<td>0.3</td>
</tr>
<tr>
<td>Meningioma</td>
<td>39</td>
<td>0.94</td>
</tr>
<tr>
<td>Chordoma</td>
<td>22</td>
<td>0.5</td>
</tr>
<tr>
<td>Metastasis</td>
<td>25</td>
<td>0.6</td>
</tr>
<tr>
<td>Squamous carcinoma</td>
<td>2</td>
<td>0.05</td>
</tr>
<tr>
<td>Gangliocytoma (with adenoma)</td>
<td>14 (13)</td>
<td>0.34 (0.31)</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>7</td>
<td>0.17</td>
</tr>
<tr>
<td>Other sarcomas</td>
<td>2</td>
<td>0.05</td>
</tr>
<tr>
<td>Granular cell tumor</td>
<td>7</td>
<td>0.17</td>
</tr>
<tr>
<td>Neurinoma</td>
<td>3</td>
<td>0.07</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>6</td>
<td>0.15</td>
</tr>
<tr>
<td>Pituicytoma</td>
<td>3</td>
<td>0.07</td>
</tr>
<tr>
<td>Ganglioglioma</td>
<td>1</td>
<td>0.02</td>
</tr>
<tr>
<td>Neurocytoma</td>
<td>1</td>
<td>0.02</td>
</tr>
<tr>
<td>Suprasellar germinoma</td>
<td>6</td>
<td>0.15</td>
</tr>
<tr>
<td>Gliomatous tumor, not classified</td>
<td>1</td>
<td>0.02</td>
</tr>
<tr>
<td>Histiocytosis of Langerhans</td>
<td>2</td>
<td>0.05</td>
</tr>
<tr>
<td>Neuroendocrine tumor, not classified</td>
<td>1</td>
<td>0.02</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>1</td>
<td>0.02</td>
</tr>
<tr>
<td>Fibroma</td>
<td>2</td>
<td>0.05</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>3</td>
<td>0.07</td>
</tr>
<tr>
<td>Hamartoma</td>
<td>3</td>
<td>0.07</td>
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<tr>
<td>Fibrous dysplasia</td>
<td>4</td>
<td>0.1</td>
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<td>Rathke’s cyst</td>
<td>76</td>
<td>1.8</td>
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<tr>
<td>Colloid cyst</td>
<td>15</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Arachnoidal cyst 9 0.22
Epidermoid cyst 10 0.24
Cyst, not classified 5 0.12
Mucocele 2 0.05
Plasma cell granuloma 1 0.02
Granulation tissue 3 0.07
Lymphocytic hypophysitis 14 0.34
Granulomatous hypophysitis 6 0.14
Granulomatous hypophysitis in generalized disease 1 0.02
Tuberculous hypophysitis 1 0.02
Peritumoral hypophysitis 2 0.05
Abscess 10 0.24
Chronic inflammation, not classified 9 0.22
Necrosis 2 0.05
Fibrosis or scar 17 0.4
Hyperplasia of ACTH cells 4 0.1
Hyperplasia of prolactin cells 6 0.15
Hyperplasia of GH cells 2 0.05
Hyperplasia of FSH/LH cells 1 0.02
Castration cells 2 0.05
Crooke cells (without adenoma) 76 1.84
Normal pituitary 53 1.3
No diagnosis (insufficient specimens) 13 0.32

Sum 4122 100

Seager et al, 2007
Pituitary Adenomas - Epidemiology

**Frequency**
Pituitary adenomas account for 10-15% of primary intracranial neoplasms.

**Prevalence**
Overall estimated prevalence of pituitary adenomas: 16.7%
- Autopsy studies: in ~14.4%
- Imaging studies: ~22.5% (Ezzat et al, 2004)

Clinically relevant PA:
- 1:1388 (1:909-1:1818) /multicentric/ (Daly et al, 2009)
- 1:1000 in a Belgian population (Daly et al, 2006)
- 0.776:1000 in a region of the UK (Fernandez et al, 2010)
- 0.04:1000 in Finland (Paappana et al, 2010).

**Incidence**
Annual incidence ranges from 0.5 to 0.7/100,000
Sex
Incidence of macroadenomas is similar between males and females
However clinical manifestations of microadenomas are more in women

Size
Microadenomas <1 cm in diameter (~50%)
Macroadenomas >1 cm (~50%), giant adenomas >4 cm

Hormone secreting vs. inactive
~70% are endocrinologically active
~30% do not have clinical syndrome of hormone access

Benign vs. malignant
99% of pituitary gland tumors are benign
0.12% pituitary carcinoma (malignant behaviour & metastases)
## Pituitary Adenomas Types

### Clinical

Table 1. Prevalence of Pituitary Adenomas in Community-Dwelling Adults

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Years of Data Collection</th>
<th>No. of Patients With Pituitary Adenomas</th>
<th>Prevalence</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prolactin-Secreting Tumor</td>
</tr>
<tr>
<td>Daly et al,(^4) 2006</td>
<td>Belgium</td>
<td>2005</td>
<td>68</td>
<td>1/1064</td>
<td>45 (66)(^a)(^5)</td>
</tr>
<tr>
<td>Fontana et al,(^6) 2009</td>
<td>Switzerland</td>
<td>2006-2007</td>
<td>44</td>
<td>1/1241</td>
<td>25 (56)</td>
</tr>
<tr>
<td>Fernandez et al,(^7) 2010</td>
<td>England</td>
<td>2006</td>
<td>63(^b)</td>
<td>1/1289</td>
<td>36 (57)</td>
</tr>
<tr>
<td>Raappana et al,(^8) 2010</td>
<td>Finland</td>
<td>1992-2007</td>
<td>164(^b)</td>
<td>1/1471</td>
<td>84 (51)</td>
</tr>
<tr>
<td>Gruppetta et al,(^9) 2013</td>
<td>Malta</td>
<td>2000-2011</td>
<td>316(^b)</td>
<td>1/1321</td>
<td>146 (46)</td>
</tr>
<tr>
<td>Tjörnstrand et al,(^10) 2014</td>
<td>Sweden</td>
<td>2001-2011</td>
<td>592(^b)</td>
<td>1/2688</td>
<td>187 (32)</td>
</tr>
<tr>
<td>Agustsson et al,(^11) 2015</td>
<td>Iceland</td>
<td>1955-2012</td>
<td>471</td>
<td>1/865</td>
<td>188 (40)</td>
</tr>
</tbody>
</table>

Average: 49.7% 34.4% 11% 3.8% 48%
### Pituitary Adenomas Types

#### Histology

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Transcription factors</th>
<th>Hormones, others</th>
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</thead>
<tbody>
<tr>
<td><strong>The Pit-1 family</strong></td>
<td></td>
<td></td>
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<tr>
<td>Somatotroph adenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Densely granulated somatotroph adenoma</td>
<td>Pit-1</td>
<td>GH, α-subunit</td>
</tr>
<tr>
<td>Sparsely granulated somatotroph adenoma</td>
<td>Pit-1</td>
<td>GH, keratin whorls (fibrous bodies)</td>
</tr>
<tr>
<td>Mammosomatotroph/mixed adenoma</td>
<td>Pit-1, ER</td>
<td>GH, PRL, α-subunit</td>
</tr>
<tr>
<td>Lactotroph adenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sparsely granulated lactotroph adenoma</td>
<td>Pit-1, ER, ?GH-repressor</td>
<td>PRL, Golgi pattern</td>
</tr>
<tr>
<td>Densely granulated lactotroph adenoma</td>
<td>Pit-1, ER, ?GH-repressor</td>
<td>PRL diffuse cytoplasmic</td>
</tr>
<tr>
<td>Acidophil stem cell adenoma</td>
<td>Pit-1, ER</td>
<td>PRL, (GH), keratin whorls (fibrous bodies)</td>
</tr>
<tr>
<td>Thyrotroph adenoma</td>
<td>Pit-1, TEF, GATA-2</td>
<td>β-TSH, α-subunit</td>
</tr>
<tr>
<td>Plurihormonal adenoma</td>
<td>Pit-1, ER, TEF, GATA-2</td>
<td>GH, PRL, β-TSH, α-subunit</td>
</tr>
<tr>
<td><strong>ACTH family</strong></td>
<td></td>
<td></td>
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<tr>
<td>Corticotroph adenoma</td>
<td>Tpit</td>
<td>ACTH, keratins</td>
</tr>
<tr>
<td><strong>Gonadotropin family</strong></td>
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</tr>
<tr>
<td>Gonadotroph adenoma</td>
<td>SF-1, ER, GATA-2</td>
<td>β-FSH, β-LH, α-subunit</td>
</tr>
<tr>
<td><strong>Unclassified adenoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone-negative/ null cell adenoma</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Unusual plurihormonal adenoma</td>
<td>?multiple</td>
<td>Multiple</td>
</tr>
</tbody>
</table>

WHO classification; Al-Shraim et al 2005
Pituitary Adenomas – Appearance

- 95%
- Etiology of most adenomas is unknown

- 5%
- Familial syndromes
Familial Pituitary Adenomas – Hereditary tumor syndromes

- Familial isolated pituitary adenoma
- Multiple endocrine neoplasia (MEN) type 1
- Carney Complex
- McCune-Albright syndrome

- Pituitary
- Parathyroid
- Myxomas
- Spotty pigmentation
- Multiple endocrine neoplasia

- Fibrous bone dysplasia, café-au-lait spots, precocious puberty
- Hyperfunctioning endocrinopathies (GH)
Familial Pituitary Adenomas – Hereditary tumor syndromes

Pituitary Adenoma → Clinical features →

- Hyperparathyroidism and/or neuroendocrine tumor and/or adrenocortical tumor
  → Screen for MEN1 mutation

- Age of onset
  - >30 years → No genetic screening suggested
  - Macroadenoma <30 years Any tumor < 18 years → Screen for AIP mutation

- Mucosal lentigines and acromegaly or ACTH-independent Cushing’s syndrome
  → Screen for PRKAR1A mutation

If negative and the patient has a PRL or GH producing adenoma

Syro et al, 2015
FIPA patients are diagnosed on average 4 yr before patients with sporadic pituitary adenomas.

FIPA families comprise approximately 2% of pituitary adenomas.

Later generations are diagnosed with pituitary adenomas at a statistically significantly younger age as compared with their parents or grandparents (on average 20 yr before).

Adenoma types:
- prolactinoma (37.5%)
- somatotropinoma (35.0%)
- NFPAs (14.5%)
- somatolactotropinomas (6.4%)
- Cushing disease (2.9%)
- gonadotropinomas (2.0%)
- plurihormonal tumors (1.2%)
- thyrotropinomas (0.5%)

Sporadic
- 66%
- 13%
- 34%
FIPA patients are diagnosed on average 4 yr before patients with sporadic pituitary adenomas.

FIPA families comprise approximately 2% of pituitary adenomas.

Later generations are diagnosed with pituitary adenomas at a statistically significantly younger age as compared with their parents or grandparents (on average 20 yr before).

**FIPA PRLoma**

more aggressive characteristics vs. sporadic adenomas, being significantly more frequently invasive and extending toward the optic chiasm.

**FIPA acromegaly**

(correspond to the previous terminology of isolated familial somatotropinoma (IFS))

having a larger adenoma diameter and tumors that have an earlier age of onset.

**FIPA NFPA**

have a significantly younger age at onset vs. sporadic counterparts (mean, 8 yr) are significantly more frequently invasive than sporadic NFPA (84.6 vs. 59.6%, respectively).

Beckers et al, 2013
AIP gene has been identified as causing a pituitary adenoma predisposition of variable penetrance that accounts for 15-20% of FIPA families.

- In all available tumor samples from the mutation carriers, the wild-type allele was lost.
- This biallelic inactivation of AIP in the tumors strengthened the assumption that AIP is likely to act as a tumor suppressor.

Beckers et al, 2013
*AIP* gene has been identified as causing a pituitary adenoma predisposition of variable penetrance that accounts for **15-20% of FIPA families**.
**AIP** gene has been identified as causing a pituitary adenoma predisposition of variable penetrance that accounts for **15-20% of FIPA families**.

Beckers et al, 2013
Relative resistance to somatostatin analogs in AIP mutation-related somatotropinomas vs. controls.
Familial Pituitary Adenomas – Hereditary tumor syndromes

Pituitary Adenoma

Clinical features

Age of onset

Hyperparathyroidism and/or neuroendocrine tumor and/or adrenocortical tumor
- >30 years
- No genetic screening suggested

Screen for MEN1 mutation

Macroadenoma <30 years
- Any tumor < 18 years
- Screen for AIP mutation

Screen for AIP mutation

Mucosal lentigines and acromegaly or ACTH-independent Cushing’s syndrome
- Screen for PRKAR1A mutation

If negative and the patient has a PRL or GH producing adenoma

Syro et al, 2015
• Prevalence: 1:30 000
• Men:women 1:1
• Patients have been diagnosed between 8-81 years of age, but before the age of 10 is rare
• Inheritance is AD
• MEN1 gene mutations can be identified in 70-95% of MEN1 patients

MEN1

Facial angiofibromas 88%
Collagenomas < 72%
Lipomas < 34%
Café au lait spots < 30%
Hypopigmentation < 11%
Gingival papules < 6%

Parathyroid >95%

Pancreas ~75%

Other ~40%

Pituitary ~40-50%

Adrenal cortex 20–70%
Meningioma 10%
Gastric NET 10%
Thymic NET < 3%
Bronchial NET < 3%

Non-functioning 20–55% (< 20)
Gastrinoma 40% (25)
Insulinoma 10% (< 8)
Glucagonoma < 1% (< 13)
VIPoma < 1(< 11)
Somatostatinoma < 1 (< 7)

Prolactinoma 20% (< 3)
Non-functioning 10% (< 3)
Acromegaly 10% (< 3)
Cushing’s disease < 5% (< 3)
TSHoma < 1%

Carroll, 2012
Prevalence: \(<1 / 1,000,000\)
Inheritance: Autosomal dominant

<table>
<thead>
<tr>
<th>Main features of Carney complex</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Pigmented Nodular Adrenocortical Disease (PPNAD)</td>
<td>25–60</td>
</tr>
<tr>
<td>Cardiac myxoma</td>
<td>30–60</td>
</tr>
<tr>
<td>Skin myxoma</td>
<td>20–63</td>
</tr>
<tr>
<td>Lentiginosis</td>
<td>60–70</td>
</tr>
<tr>
<td>Multiple blue nevus</td>
<td></td>
</tr>
<tr>
<td>Breast ductal adenoma</td>
<td>25</td>
</tr>
<tr>
<td>Testicular tumors (LCCSCT: Large-Cell Calcifying Sertoli Cell Tumor) (in male)</td>
<td>33–56</td>
</tr>
<tr>
<td>Ovarian cyst (in female)</td>
<td>20–67</td>
</tr>
<tr>
<td><strong>Acromegaly</strong></td>
<td><strong>10</strong></td>
</tr>
<tr>
<td>Thyroid tumor</td>
<td>10–25</td>
</tr>
<tr>
<td>Melanotic schwannoma</td>
<td>8–18</td>
</tr>
<tr>
<td>Osteochondromyxoma</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

GH hyperplasia
GH adenoma – 10-15%

Bertherat, 2006
Prevalence: 1/100,000 - 1/1,000,000

Somatic mutations of the GNAS gene, specifically mutations in the cAMP regulating protein, Gs alpha.

**Clinical triad:**
- fibrous dysplasia of bone (FD),
- café-au-lait skin spots, and
- precocious puberty (PP)

**Other hyperfunctioning endocrinopathies** may be involved:
- hyperthyroidism,
- GH and PRL excess are common (21%),
- Cushing syndrome (mostly neonatal)
- renal phosphate wasting

**Diagnosis:**
Plain radiographs are often sufficient to make the diagnosis of FD and biopsy of FD lesions can confirm the diagnosis.

While MAS is rare, FD is not.
MAS = FD + at least one of the typical hyperfunctioning endocrinopathies and/or café-au-lait spots, with almost any combination possible

Dumitrescu & Collins, 2008
Pituitary Adenomas – Appearance

- 95%
- Etiology of most adenomas is unknown

- 5%
- Familial syndromes
Pituitary Adenoma - Clinical Manifestations

The presenting symptoms may be due to

- Hormonal malfunction
- Due to local tumour growth and pressure effect

Hypopituitarism

Hyperpituitarism (hormone overproduction)
Pituitary Adenoma - Clinical Manifestations

Mass effect

**Increased intrasellar pressure**
An expanding mass within a bony structure
Stretching of meninges

\[ \text{headache (25\%)} \]

Lateral extension $\rightarrow$ *the cavernous sinuses*
(We have reported a **14\%** incidence of symptoms related to *cranial nerve pressure*, although evidence for cavernous sinus involvement was present in **48\%** of patients: ptosis, ophtalmoplegia and diplopia, may be reversible with surgical decompression)

**Suprasellar extension** $\rightarrow$ pressure on the *optic chiasm* (**50\%**)
(visual field defects, bitemporal haemianopsia, prolonged pressure: optic nerve atrophy)

Haemorrhagic infarction (tumor *apoplexy*)
$\rightarrow$ resulting in sudden, severe headaches, visual impairment and hypopituitarism.

Greenman et al, 2009
Pituitary Adenoma - Clinical Manifestations

- compress the normal pituitary gland and cause pituitary failure

  Symptoms of hypopituitarism may include:
  - Nausea and vomiting
  - Loss of appetite
  - Weight loss
  - Fatigue, decreased energy
  - Decreased mental function
  - Dizziness
  - Joint pains
  - Women: infertility, irregular or nonexistent menses
  - Men: infertility, impotence in men, loss of body and facial hair
  - Loss of sexual drive
Pituitary Adenomas Types

**Clinical**

<table>
<thead>
<tr>
<th>Adenoma Type</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactinoma</td>
<td>49.7</td>
</tr>
<tr>
<td>Nonfunctioning adenoma</td>
<td>34.4</td>
</tr>
<tr>
<td>GH secreting adenoma</td>
<td>11.0</td>
</tr>
<tr>
<td>ACTH secreting adenoma</td>
<td>3.9</td>
</tr>
<tr>
<td>TSH secreting adenoma</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
Prolactinoma

- 40-50% of all PA
- It can appear 2-80 yrs (uncommon in children)
- More common in **women**: peak incidence in childbearing years
- Prolactinomas are generally classified according to size (micro/macro)

- Over **90% are small** that rarely increase in size

- Occasionally, these adenomas can be aggressive or locally invasive and cause compression of vital structures

- Adenomas:
  - PRLoma
  - mixed PRL+GH secreting adenoma → acromegaly + hyperPRL
  - PRL + TSH/ACTH → uncommon
  - Occasionally can be part of MEN1 or FIPA
Prolactin

Breast feeding
Chest wall stimulation/trauma
Stress
Sleep

Hth

TRH
neurophysin
substance P
E2

PA

Dopamine

Somatostatin

PRL

• Induces proliferation of ductal and acinar cells in breast
• Induces milk production by breast alveolar epithelium
• Secondary effect on gonadal function

There is no evidence linking oestrogen therapy/OAC to the formation of prolactinomas
Physiology

- interrupts pulsatile secretion of GnRH
- inhibits FSH, LH release
- directly impairs gonadal steroidogenesis

Symptoms of hyperprolactinaemia

- lactational amenorrhea
- oligo/amenorrhea
- galactorrhea
- infertility (anovulatory in women)
- decreased libido
Differential Diagnosis of Hyperprolactinaemia

- Sellar/parasellar masses
- Granulomatosus infiltration of hypothalamus
- Head trauma
- Large PA (other than PRLoma)

- Impairment of hypothalamic production of dopamine
- Compression of pituitary stalk (inhibit dopamine transport)

- Chronic renal failure
- Chronic hepatic failure

- Decreased clearance of PRL

- Polycystic ovarian syndrome is commonly associated with hyperprolactinaemia

- Primary hypothyroidism (usually mild)

- Elevated TRH

- Idiopathic

- Drug effect
## Differential Diagnosis of Hyperprolactinaemia

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Medication types/examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics/neuroleptics</td>
<td>Phenothiazines</td>
</tr>
<tr>
<td></td>
<td>Butyrophenones</td>
</tr>
<tr>
<td></td>
<td>Atypical antipsychotics</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Tricyclic and tetracyclic antidepressants</td>
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<tr>
<td></td>
<td>Monoamine oxidase (MAO) inhibitors</td>
</tr>
<tr>
<td></td>
<td>Selective serotonin re-uptake inhibitors (SSRI)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Opiates</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
</tr>
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<td>Antihypertensive medications</td>
<td>Verapamil</td>
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<tr>
<td></td>
<td>Methyldopa</td>
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<td></td>
<td>Reserpine</td>
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<tr>
<td>Gastrointestinal medications</td>
<td>Metoclopramide</td>
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<tr>
<td></td>
<td>Domperidone</td>
</tr>
<tr>
<td></td>
<td>H2 blockers</td>
</tr>
<tr>
<td>Protease inhibitors?</td>
<td></td>
</tr>
<tr>
<td>Oestrogens</td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Molitch 2005.*

Casanueva et al, 2006
Diagnosis of Prolactinoma – clinical assessment

Diagnosis of PRLoma
1 – basal PRL level
2 – imaging
3 – exclude drugs and technical problems

Symptoms → Hyperprolactinemia
(basal sample)*

MRI

Idiopathic or Micro

Symptoms
Absent
Follow-up

Macro

Present

Treatment

*rule out drug induced hyperprolactinaemia and technical problems

Fig. 1 Recommended diagnostic algorithm for prolactinomas.

Casanueva et al, 2006
Diagnosis of Prolactinoma – laboratory findings

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>W</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal range</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 20 ug/l</td>
<td>&lt; 25 ug/l</td>
</tr>
<tr>
<td></td>
<td>&lt; 424 mIU/l</td>
<td>&lt; 530 mIU/l</td>
</tr>
</tbody>
</table>

| **Modest elevation** | Normal – 150 ug/l – 3000 mIU/l | Interference with dopamine action (drugs, estrogen, idiopathic) |
|                      |                               | Microadenoma                           |
|                      |                               | PA other than PRLoma (stalk compr)     |

| **High**            | > 150 ug/l                | Patient has PRLoma                     |
|                     | > 3000 mIU/l              |                                             |
|                     | > 250-1000 ug/l           | Patient has macroPRLoma                 |
|                     | > 5000-20000 mIU/l        |                                             |

Casanueva et al, 2006
Diagnosis of Prolactinoma – pifalls

1. Withdraw the drug at least for 72 h
2. A single measurement of PRL is adequate for dg
3. But if PRL is not diagnostic (moderate) → sampling can be repeated on another day
4. Pregnancy is not always known/communicated → test should be obtained
5. macroPRL (complex of PRL-IgG, reduced bioactivity, reduced rate of clearance)
6. Hook effect

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Smith et al, 2007
Prolactinoma – Treatment Algorithm

Dopamine Agonist

- Controlled
  - Repeat PRL
  - Visual Field
  - MRI
     - Taper & stop?
       - Controlled
       - Relapse
         - Follow-up
         - Restart treatment

- Uncontrolled
  - Another DA
    - Uncontrolled
      - Surgery
      - Uncontrolled
        - Radiotherapy

- Intolerant
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Nonfunctioning pituitary adenomas (NFPA)

- One third of all PA
- Some of them are incidentally found microadenomas
- At the time of presentation 60-70% of patients have visual-field defect (Jaffe et al, 2006)

### Table 2
Clinical characteristics of NFPA patients.

<table>
<thead>
<tr>
<th></th>
<th>Nomikos et al¹⁵</th>
<th>Losa et al¹⁶</th>
<th>Chang et al¹⁷</th>
<th>Ferrante et al⁵¹</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>721</td>
<td>491</td>
<td>663</td>
<td>295</td>
<td>2170</td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
<td>54.2 ± 19</td>
<td>–</td>
<td>53 (median)</td>
<td>50.4 ± 14.1</td>
<td></td>
</tr>
<tr>
<td><strong>Gender (M/F)</strong></td>
<td>401/320</td>
<td>276/215</td>
<td>394/269</td>
<td>161/134</td>
<td>1232/938 (56.7% M)</td>
</tr>
<tr>
<td><strong>Incidental finding</strong></td>
<td>57 (7.9%)</td>
<td>57 (11.6%)</td>
<td>49 (7.4%)</td>
<td>–</td>
<td>163/1875 (8.7%)</td>
</tr>
<tr>
<td><strong>Headaches</strong></td>
<td>70 (9.7%)</td>
<td>–</td>
<td>212 (32%)</td>
<td>122 (41.4%)</td>
<td>404/1679 (24%)</td>
</tr>
<tr>
<td><strong>Visual deficits</strong></td>
<td>222 (30.8%)</td>
<td>287/486 (59.1%)</td>
<td>327 (49%)</td>
<td>200 (67.8%)</td>
<td>1036/2170 (47.7%)</td>
</tr>
<tr>
<td><strong>Pressure on cranial nerves</strong></td>
<td>–</td>
<td>22 (4.5%)</td>
<td>26 (3.9%)</td>
<td>–</td>
<td>48/1154 (4.2%)</td>
</tr>
<tr>
<td><strong>Apoplexy</strong></td>
<td>27 (3.7%)</td>
<td>48 (9.8%)</td>
<td>24 (3.6%)</td>
<td>–</td>
<td>99/1875 (5.3%)</td>
</tr>
<tr>
<td><strong>Symptoms of</strong></td>
<td>345 (47.8%)</td>
<td>–</td>
<td>342 (51.6%)</td>
<td>118 (40%)</td>
<td>805/1679 (48%)</td>
</tr>
<tr>
<td><strong>Hypopituitarism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Documented</strong></td>
<td>614 (85%)</td>
<td>–</td>
<td>–</td>
<td>183 (62%)</td>
<td>797/1016 (78.4%)</td>
</tr>
<tr>
<td><strong>Hypogonadism</strong></td>
<td>512/659 (77.7%)</td>
<td>335/474 (70.7%)</td>
<td>128 (43.3%)</td>
<td>975/1261 (77.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hypoadrenalism</strong></td>
<td>230 (31.9%)</td>
<td>115/478 (24.1%)</td>
<td>77 (26.2%)</td>
<td>422/1494 (28.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hypothyroidism</strong></td>
<td>129/658 (19.6%)</td>
<td>116/462 (25.1%)</td>
<td>72 (24.5%)</td>
<td>317/1415 (22.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hyperprolactinemia</strong></td>
<td>199 (27.6%)</td>
<td>251/462 (54.3%)</td>
<td>–</td>
<td>82 (27.6%)</td>
<td>532/1478 (35.9%)</td>
</tr>
</tbody>
</table>

Greenman et al, 2009
Nonfunctioning pituitary adenomas (NFPA)

- Adenomas - heterogeneity:
  - ~85% arises from gonadotope cells
    - Most of them are positive for intact glycoprotein hormones (FSH, LH, TSH) or subunits (αSU, β-FSH, β-LH, β-TSH)
  - ~15% silent adenomas (silent adenomas, which express hormones as detected by immunocytochemistry, but do not secrete them)
    - silent GH, prolactin and TSH tumours have been reported, the majority express ACTH
    - ~10% null cell adenoma

### Table 1
Clinico-pathological classification of NFPA.

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Transcription factors</th>
<th>Hormone staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonadotroph adenomas</td>
<td>SF-1, GATA-2, ER</td>
<td>β-FSH, β-LH, α-subunit</td>
</tr>
<tr>
<td>Silent adenomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silent somatotroph adenomas</td>
<td>Pit-1</td>
<td>GH</td>
</tr>
<tr>
<td>Silent prolactinomas</td>
<td>Pit-1, ER</td>
<td>PRL</td>
</tr>
<tr>
<td>Silent thyrotroph adenomas</td>
<td>Pit-1, TEF, GATA-2</td>
<td>β-TSH, α-subunit</td>
</tr>
<tr>
<td>Silent corticotroph adenomas</td>
<td>Tpit</td>
<td>ACTH</td>
</tr>
<tr>
<td>Null cell adenomas</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Silent subtype 3 adenomas</td>
<td></td>
<td>Multiple</td>
</tr>
</tbody>
</table>

SF-1, steroidogenic factor-1; ER, estrogen receptor; Pit-1, pituitary transcription factor-1; TEF, thyrotropin embryonic factor. Adapted from Asa et al.¹².
The correct identification of a pituitary mass being a nonfunctional adenoma can be difficult.

**Pituitary Incidentaloma: An Endocrine Society Clinical Practice Guideline**

Pamela U. Freda, Albert M. Beckers, Laurence Katzenelson, Mark E. Molitch, Victor M. Montori, Kalmon D. Post, and Mary Lee Vance

1.1.1 We recommend that all patients with a pituitary incidentaloma, including those without symptoms, undergo clinical and laboratory evaluations for hormone hypersecretion (111111).

1.1.2 We recommend that patients with a pituitary incidentaloma with or without symptoms also undergo clinical and laboratory evaluations for hypopituitarism (111111).

1.1.3 We recommend that all patients presenting with a pituitary incidentaloma abutting the optic nerves or chiasm on magnetic resonance imaging (MRI) undergo a formal visual field (VF) examination (111111).

1.1.4 We recommend that all patients have a MRI scan, if possible, to evaluate the pituitary incidentaloma [if the incidentaloma was initially only diagnosed by computed tomography (CT) scan] to better delineate the nature and extent of the incidentaloma (111111).
Diagnosis / Differential diagnosis – NFPA

The correct identification of a pituitary mass being a nonfunctional adenoma can be difficult.

1. Exclude other sellar masses - imaging

   rest cell tumors (*craniopharyngioma, Rathke’s cleft cyst, chordoma and others*), gliomas, meningioma, germ cell tumors, granulomatous diseases, metastatic tumors and other lesions....

2. Measure gonadotropin(FSH,LH)/free SUs - lab

   • *In a minority* of patients, intact gonadotropins, mainly FSH, may be detected in basal conditions in vivo, but hormone-related symptoms are rare.
   
   • Because gonadotropins and free SUs are elevated in *primary gonadal failure* and in *postmenopausal women*, interpretation of these baseline data must be completed in the context of the patient’s gonadal hormone status.
   
   • Measurement of gonadotropin subunits is not routinely available in clinical labs

3. Measure PRL (stalk compression)

   • Modest serum prolactin elevations (generally <200 ng/ml) occur in the majority of patients
Diagnosis / Differential diagnosis – NFPA

The correct identification of a pituitary mass being a nonfunctional adenoma can be difficult.

4. iv. TRH test - can help differentiate pituitary adenoma from other lesions
    • Paradoxical increases in FSH, LH and/or free α/β SU
    • ~40% of NFPA patients have a positive response to TRH
    • Helpful in establishing that a pituitary mass in a hypogonadal patient is a glycoprotein secreting adenoma.

5. ACTH measurements – Endocrine Society Guideline:
    • „The Task Force does not recommend the routine measurement of plasma ACTH levels in patients with incidentalomas.
    • However, some of the Task Force members often measure ACTH because a small percentage of incidentalomas may be silent corticotroph tumors, and occasionally plasma ACTH levels are elevated in patients harboring these tumors despite the lack of clinical manifestations of cortisol excess.”
Treatment – NFPA

microadenomas – tumor growth is observed in 3.2–12.5%
macroadenomas – tumor enlargement was reported in up to 50%

Jaffe et al, 2006
Freda et al, 2011
## Pituitary Adenomas Types

### Clinical

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GH secreting adenomas

- Acromegaly: disproportionate skeletal, tissue, and organ growth
- Prevalence: 60 / million
- Incidence: 3-4 / million / year.
- „the diagnosis is invariably preceded by about 10 years of active but unrecognized disease” – it develops insidiously over many years

Image of limestone relief portrait of Egyptian Akhenaten, circa 1365 BCE, showing jaw prognathism and thickened lips.
Wikipedia (http://commons.wikimedia.org/wiki/File:ReliefPortraitOfAkhenaten01.png)
Source: Altes Museum, Berlin, Germany.
GH secreting adenomas

• Sporadic
  • *Densely granulated* - pure GH secreting, usually in older patients with minimally elevated GH levels
  • *Sparsely granulated* - pure GH secreting, usually in younger patients with high GH levels and aggressive growth
  • *Mixed GH and PRL* - GH&PRL secretion by monomorphic mammosomatotrophes or mixed somatotrophs and lactotrophs. May occur with gigantism.
  • *Acidophilic stem cell adenoma* - GH&PRL secretion by precursor cell tumor, usually aggressive and may occur in younger patients with gigantism
  • *Plurihormonal GH adenoma* - Secretes GH plus PRL, ACTH or rarely, TSH
  • *Ectopic adenomas* - arises in remnant nasopharyngeal pituitary tissue
  • *Empty sella tumor* - tumor remnants secreting GH arising in rim of pituitary tissue
  • *GH-cell carcinoma* - Exceedingly rare with extraramial metastases
  • *GH secreting extrapituitary tumor* - Abdominal, pancreatic, or lymphoma; very rare
  • *Mc Cune-Albright syndrome*

• Familial
  • *MEN 1, FIPA, Carney complex*

• GHRH excess
  • *Hypothalamic* (harmartoms, gangliocytoma, glyoma)
  • *Extrahypothalamic* (Pancreatic carcinoids, bronchial carcinoma, etc)
Born in Alton, Illinois in 1918. “The Giant of Illinois.” By the time he was 8, he was already 6 ft 2 in. This condition led to Wadlow’s height constantly increasing throughout his life.

Born in Tennessee in 1868, Rogan suffered a sudden growth spurt at the age of 13 and gained height rapidly.

Born in 1932 in Buffalo, New York, John Carroll was referred to as the “Buffalo Giant” in medical journals. When he was 16, Carroll’s incredible growth spurt kicked in, and it didn’t stop until his eventual death in 1969.
## Impact of long-term GH and IGF1 exposure

<table>
<thead>
<tr>
<th>Organ/tissue</th>
<th>Clinical feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone and joint</td>
<td>Acral changes, gigantism, prognathism, arthritis, osteopenia, vertebral fractures, carpal tunnel syndrome</td>
</tr>
<tr>
<td>Heart</td>
<td>Cardiomyopathy, hypertension, arrhythmias, valvulopathy, heart failure</td>
</tr>
<tr>
<td>Skin</td>
<td>Tags, excessive oily perspiration</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Insulin resistance, diabetes</td>
</tr>
<tr>
<td>Lung</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Kidney</td>
<td>Antinatriuresis, fluid retention, increased aldosterone, renal failure</td>
</tr>
<tr>
<td>Gonads</td>
<td>Hypogonadism</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Goiter</td>
</tr>
<tr>
<td>Muscle</td>
<td>Proximal myopathy</td>
</tr>
<tr>
<td>Colon</td>
<td>Polyps</td>
</tr>
<tr>
<td>Fat</td>
<td>Lipolysis</td>
</tr>
<tr>
<td>Visceromegaly</td>
<td>Tongue, thyroid, salivary gland, liver, spleen, kidney, prostate</td>
</tr>
</tbody>
</table>

- **macroglossia**
- Increased thickness of heel soft tissue
- Kyphotic spine
- Anchor-like shape of the diastal phalange
Acromegaly - comorbidities

• 15-38% - DM type 2, impaired glucose tolerance
• 33-46% - hypertension – predominance of diastolic BP elevation
• increased TG, LDL, Lp(a)
• cardiac hypertrophy, arrhythmias, diastolic dysfunction
• 69% - sleep apnea
• 19.3% - colon polyps under age of 40 (vs. 4.4% in normal)
• 54% , 18-20% - thyroid nodules, goiter
• 20-64% - carpal tunnel sy
• 77% - joint problems – arthritis
• vertebral compression, fractures
• hypogonadism

• 10 years reduction in life expectancy
• approximate 2-fold excess mortality
Acromegaly – Lab test

**GH production**
- pulstile
- diurnal

**Random GH**
- 1 GH is not = GH
- Do not measure, but if you do, do it at least 3x!

**Diurnal rhythm assessment**
- 5x, in every 3h

**Functional tests**
- Suppression: OGTT (GH+glucose!!)

A nadir serum GH level <1g/L within 2 hours after 75 g of oral glucose usually excludes the diagnosis
Acromegaly – Lab test

IGF-1 – quite stable throughout the day
Normal range is given for man/women and for different age groups

~98% of IGF-1 is always bound to one of 6 binding proteins (IGF-BP)
IGFBP-3, the most abundant protein, accounts for 80% of all IGF binding

False positive/high values: pregnancy, late-stage adolescence
Acromegaly - Diagnosis

1 - Measure IGF-1 level in patients with **typical clinical manifestations**
   - (without the typical manifestations of acromegaly, but who have several of these associated conditions: sleep apnea syndrome, type 2 diabetes mellitus, debilitating arthritis, carpal tunnel syndrome, hyperhidrosis, and hypertension)

2 - Measure IGF-1 level to rule out acromegaly in a patient **with a pituitary mass**

3 - We recommend **against** relying on the use of random GH levels to diagnose acromegaly

4 - In patients with elevated or equivocal serum IGF-1 levels, we recommend **confirmation** of the diagnosis by finding **lack of suppression of GH**

5 - **Following biochemical diagnosis** of acromegaly → imaging (tumor size and appearance, as well as parasellar extent) (**MRI ± VF**)
Management of Acromegaly

Transsphenoidal surgery (most patients)

Considerations
- If majority of tumor unresectable and no chiasmal compression
- Poor surgical candidate

Surgical debulking

Persistent disease (Incomplete surgery)

Medications
- SRL (for most)
- DA (mild disease)
- Pegvisomant

- Partial clinical and biochemical response to maximal doses
  - Consider combination therapy of above drugs
- No clinical and biochemical response
  - Consider alternative monotherapy

Ineffective or intolerable medications

Consider SRT
(conventional radiation if not candidate)

Remission
- Annual IGF-1 and random GH
- Consider OGTT

MRI (If clinical or biochemical signs of recurrence)

Radiation therapy may be considered at any point following incomplete surgery
Summary

Overall estimated prevalence of pituitary adenomas: 16.7%
Clinically relevant PA: 1:1388

Accounts for 10-15% of all intracranial tumors

99% of pituitary gland tumors are benign

95% sporadic, 5% familial (MEN type 1, FIPA, Carney complex)

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Summary

Clinical manifestation

- mass effect – headache, visual defects
- symptoms of hypopituitarism

<table>
<thead>
<tr>
<th>Growth hormone deficiency</th>
<th>Gonadotrophin deficiency</th>
<th>Thyrotropin deficiency</th>
<th>Corticotrophin deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>Adults</td>
<td>Adults</td>
<td>Adults</td>
</tr>
<tr>
<td>↑CVR disease</td>
<td>Diminished libido and impotence</td>
<td>weight gain</td>
<td>General weight loss</td>
</tr>
<tr>
<td>↓reduced muscle strength</td>
<td>Infertility</td>
<td>lack of energy</td>
<td>lack of energy</td>
</tr>
<tr>
<td>↑increased cholesterol</td>
<td></td>
<td>cold intolerance</td>
<td>medical emergency</td>
</tr>
<tr>
<td>Infants</td>
<td>Children</td>
<td>constipation</td>
<td>Severe adrenal insufficiency</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Absence of puberty</td>
<td></td>
<td>medical emergency</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td>Surgical removal of PA</td>
</tr>
<tr>
<td>growth failure</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

panhypopituitarism
Summary

Clinical manifestation

- mass effect – headache, visual defects
- symptoms of hypopituitarism
- symptoms of hormone overproduction

Melmed et al, 2003
Summary

Clinical manifestation
• mass effect – headache, visual defects
• symptoms of hypopituitarism
• hormone overproduction

Diagnosis
• symptoms
• lab test (hormonal evaluation)
• imaging (MRI) → VF