OUTLINE:

• Introduction

• Sellar and parasellar mass
  • Different pathology
  • Presentation
  • Approach to Sellar and parasellar mass
  • Overview of functional tumors
    • Prolactinoma
    • Acromegaly
    • Cushing syndrome

• Take home message
INTRODUCTION:

The pituitary gland, (hypophysis) is an endocrine gland about the size of a pea and weighing 0.5 grams in humans.

- Anterior
- Intermediate
- Posterior
INTRODUCTION:
The *prevalence* of pituitary adenomas per 100,000 was fourfold higher than previous estimates:

- All adenomas – 77.6
  - Lactotroph adenomas – 44.4
  - Nonfunctioning adenomas – 22.2
  - Somatotroph adenomas – 8.6
  - Corticotroph adenomas – 1.2
CLASSIFICATION:

• Size:
  • Microadenoma
  • Macroadenoma

• Cell of origin:
  • Gonadotroph adenomas
  • Thyrotoph adenomas
  • Corticotroph adenomas
  • Lactotroph adenomas
  • Somatotroph adenomas
  • Plurihormonal adenomas: //
    Lactotroph/somatotroph adenoma combinations

• Function:
  • Functional
  • Nonfunctional

• Location:
  • Intrasellar
  • Extrasellar
  • Mixed
TUMOR EXTENSION CLASSIFICATION

Noninvasive (enclosed)

Invasive

Grade 0
Grade I
Grade II
Grade III
Grade IV

Symmetrical

Asymmetrical

A
B
C
D
E

HARDY CLASSIFICATION SYSTEM

KNOSP CLASSIFICATION SYSTEM

Fig. 9.20 Classification systems characterizing pituitary adenomas. (A) Hardy classification system. Seila
CAUSES (1):

• **Benign Tumors:**

  • **Pituitary adenomas** are the most common cause of sellar masses (about 90%)

  • **Other disorders**, which are often difficult to distinguish from pituitary adenomas by imaging, include physiologic enlargement of the pituitary and benign and malignant tumors

    • **Pituitary hyperplasia**:

      • Lactotroph hyperplasia

      • Thyrotroph and gonadotroph hyperplasia

      • Somatotroph hyperplasia

  • **Other benign tumors**

    • Craniopharyngiomas, meningiomas, and, less commonly, pitucytomas
CAUSES (2):

- **Malignant tumors**:  
  - **Primary**: germ cell tumors (ectopic pinealomas), sarcomas, chordomas, lymphomas and rarely Pituitary carcinomas.  
  - **Metastatic disease** — Metastases to the hypothalamus and pituitary gland account for 1 to 2% of sellar masses (most commonly: breast cancer in women / lung cancer in men)

- **Cysts** — Several types of cysts can occur in the sellar and/or suprasellar area, including Rathke's cleft, arachnoid, and dermoid cysts

- **Abscess**: only one third have features suggestive of infection (fever, leukocytosis, meningismus)

- **Arteriovenous fistula of the cavernous sinus**

- **Hypophysitis**: usually occurs in late pregnancy or the postpartum period
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients (%)</th>
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<tbody>
<tr>
<td>Pituitary tumors</td>
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<tr>
<td>Hormone-secreting tumors</td>
<td>533 (48)</td>
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<tr>
<td>Nonsecreting tumors</td>
<td>483 (43)</td>
</tr>
<tr>
<td>Nonpituitary sellar/parasellar lesions</td>
<td>104 (9)</td>
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<tr>
<td>Cell rest tumors</td>
<td></td>
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<tr>
<td>Craniopharyngioma</td>
<td>17 (16)</td>
</tr>
<tr>
<td>Rathke's cleft cyst</td>
<td>35 (33)</td>
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<tr>
<td>Epidermoid</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Chordoma</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Other cyst</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Benign lesions</td>
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<tr>
<td>Meningioma</td>
<td>8 (8)</td>
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<td>Metastatic tumors</td>
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<tr>
<td>Breast</td>
<td>11 (10)</td>
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<td>Prostate</td>
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<td>Lung</td>
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<td>Parotid</td>
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<tr>
<td>SNUC*</td>
<td>1</td>
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<tr>
<td>Unknown primary</td>
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<tr>
<td>Lymphoma</td>
<td>1 (1)</td>
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<td>Vascular lesions</td>
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<tr>
<td>Aneurysm</td>
<td>1 (1)</td>
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<tr>
<td>Granulomatous, infectious, and inflammatory</td>
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<tr>
<td>Sarcoid</td>
<td>1 (1)</td>
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<tr>
<td>Granulomatous hypophysitis</td>
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<tr>
<td>Pituitary abscess</td>
<td>1 (1)</td>
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<tr>
<td>Mucocele</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Lymphocytic hypophysitis</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Miscellaneous (CSF-related)</td>
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<tr>
<td>Arachnoid cyst</td>
<td>4 (4)</td>
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<tr>
<td>TOTAL</td>
<td>1120</td>
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<td>Table 2. CLASSIFICATION OF PARASELLAR AND INTRASELLAR NONPITUITARY LESIONS</td>
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<td>------------------------------------------------</td>
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<tr>
<td><strong>Cell rest tumors</strong></td>
<td><strong>Benign lesions</strong></td>
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<tr>
<td>Craniopharyngioma</td>
<td>Meningioma (olfactory, tuberculum,</td>
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<tr>
<td>Rathke’s cleft cyst</td>
<td>diaphragms, sphenoid wing)</td>
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<td>Epidermoid (cholesteatoma)</td>
<td>Enchondroma</td>
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<tr>
<td>Infundibuloma</td>
<td><strong>Metastatic tumors</strong></td>
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<tr>
<td>Chordoma</td>
<td><strong>Vascular lesions</strong></td>
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<tr>
<td>Lipoma</td>
<td>Granulomatous, infectious, and inflammatory</td>
</tr>
<tr>
<td>Colloid cyst</td>
<td>Pituitary abscess, bacterial and fungal</td>
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<tr>
<td><strong>Primitive germ cell tumors</strong></td>
<td>Sarcoi</td>
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<td>Germinoma</td>
<td>Tuberculosis</td>
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<td>Dermoid</td>
<td>Giant cell granuloma</td>
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<td>Teratoma</td>
<td>Echinococcal cyst</td>
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<tr>
<td>Atypical teratoma (dysgerminoma)</td>
<td>Mucocele (sphenoid)</td>
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<tr>
<td>Ectopic pinealoma</td>
<td>Histiocytosis X</td>
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<tr>
<td>Gliomas</td>
<td>Lymphocytic hypophysitis</td>
</tr>
<tr>
<td><strong>Chiasmatic-optic glioma</strong></td>
<td><strong>Miscellaneous (CSF-related)</strong></td>
</tr>
<tr>
<td>(astrocytoma, hypothalamic glioma)</td>
<td>Benign intracranial hypertension</td>
</tr>
<tr>
<td></td>
<td>(pseudotumor cerebri)</td>
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<tr>
<td>Oligodendroglioma</td>
<td>Empty sella syndrome</td>
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<tr>
<td>Ependymoma</td>
<td>Arachnoid cyst</td>
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<tr>
<td>Infundibuloma</td>
<td>Suprasellar-chiasmatic arachnoiditis</td>
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<tr>
<td>Astrocytoma</td>
<td></td>
</tr>
<tr>
<td>Microglioma</td>
<td></td>
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</table>
PRESENTATIONS OF SELlar AND PARASELLAR MASS

- Hormonal abnormalities (under- or oversecretion of pituitary hormones)
- Neurologic symptoms, such as visual impairment or headache
- Incidental finding on MRI performed for some other reason
SECRETORY TUMORS
PROLACTIN-SECRETING ADENOMAS

- The most common
- Annual incidence of approximately 30 per 100,000 population.
- Female > Male
- Micro > Macro
ACROMEGALY

The prevalence range from 28 to 137 cases per million.

Macro > Micro

The diagnosis of acromegaly can be delayed by a mean of approximately 10 years after the onset of symptoms.
Fig. 5 | Progressive changes in facial appearance in a patient with acromegaly. On the basis of an analysis of these
Fig. 1 | Timeline of the major discoveries in acromegaly research. The term 'acromegaly' was used for the first time in 1886 by the French neurologist Pierre Marie to describe the characteristic clinical features of a woman with the disease.
Fig. 2 | The main clinical features of acromegaly. Although enlargement of the extremities and facial features are the most obvious visible outward manifestations of the disease, many other comorbidities and complications occur in patients with acromegaly, including cardiovascular, metabolic, endocrine, gastrointestinal, respiratory
Management of Acromegaly

Transsphenoidal surgery (most patients)

- Remission
  - Annual IGF-1 and random GH
  - Consider OGTT
  - MRI (If clinical or biochemical signs of recurrence)

- Persistent disease (Incomplete surgery)
  - Consider SRT (conventional radiation if not candidate)

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

Surgical debulking

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
A personalized approach to acromegaly management. A personalized approach to disease management relies on integrating various data, including patient...
<table>
<thead>
<tr>
<th>Cause</th>
<th>Prevalence (%)</th>
<th>Hormonal Products</th>
<th>Clinical Features</th>
<th>Pathologic Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excess GH Secretion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary</td>
<td>98</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Densely granulated GH cell adenoma</td>
<td>30</td>
<td>GH</td>
<td>Slow growing, clinically insidious</td>
<td>Resemble normal somatotrophs, numerous large secretory granules</td>
</tr>
<tr>
<td>Sparsely granulated adenoma</td>
<td>30</td>
<td>GH</td>
<td>Rapidly growing, often invasive</td>
<td>Cellular pleomorphism, characteristic ultrastructure</td>
</tr>
<tr>
<td>Mixed GH cell and PRL cell adenoma</td>
<td>25</td>
<td>GH and PRL</td>
<td>Variable</td>
<td>Densely granulated somatotrophs, sparsely granulated lactotrophs</td>
</tr>
<tr>
<td>Mammarysomatotroph cell adenoma</td>
<td>10</td>
<td>GH and PRL</td>
<td>Common in children; gigantism, mild hyperprolactinemia</td>
<td>Both GH and PRL in same cell, often same secretory granule</td>
</tr>
<tr>
<td>Acidophil stem cell adenoma</td>
<td></td>
<td>PRL and GH</td>
<td>Rapidly growing, invasive, hyperprolactinemia dominant</td>
<td>Distinctive ultrastructure, giant mitochondria</td>
</tr>
<tr>
<td>Plurihormonal adenoma</td>
<td></td>
<td>GH (PRL with αGSU, FSH/LH, TSH, or ACTH)</td>
<td>Often secondary hormonal products are clinically silent</td>
<td>Variable; either monomorphic or plurimorphous</td>
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<tr>
<td>GH cell carcinoma or metastases</td>
<td></td>
<td>GH</td>
<td>Usually aggressive</td>
<td>Documented metastasis</td>
</tr>
<tr>
<td>MEN1 (adenoma)</td>
<td></td>
<td>GH or PRL</td>
<td>Pancreatic, parathyroid, or pituitary tumors</td>
<td>Adenoma</td>
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<tr>
<td>McCune-Albright syndrome</td>
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<td>GH, PRL</td>
<td>Classic triad</td>
<td>Hyperplasia</td>
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<tr>
<td>Ectopic sphenoid or parapharyngeal sinus pituitary adenoma</td>
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<td>GH</td>
<td>Ectopic mass</td>
<td>Adenoma</td>
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<tr>
<td>Familial acromegaly</td>
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<td>GH</td>
<td>Young patients</td>
<td>Large adenomas</td>
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<td>Carney syndrome</td>
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<td>GH</td>
<td>Classic syndrome</td>
<td>Adenoma</td>
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<tr>
<td><strong>Extrapituitary Tumor</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Pancreatic islet cell tumor</td>
<td>&lt;1</td>
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<td></td>
<td></td>
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<tr>
<td><strong>Excess GHRH Secretion</strong></td>
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<td></td>
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<tr>
<td>Central—hypothalamic hamartoma, choristoma, ganglioneuroma</td>
<td>&lt;1</td>
<td></td>
<td>Hypothalamic mass</td>
<td>Somatotroph hyperplasia</td>
</tr>
<tr>
<td>Peripheral—bronchial carcinoid, pancreatic islet cell tumor; small cell lung cancer, adrenal adenoma, medullary thyroid carcinoma, pheochromocytoma</td>
<td>1</td>
<td>GH, PRL</td>
<td>Systemic features</td>
<td>Somatotroph hyperplasia, rarely adenoma</td>
</tr>
</tbody>
</table>
Association of different pathologic subtypes of growth hormone producing pituitary adenoma and remission in acromegaly patients: a retrospective cohort study

Maryam Dehghani 1, Zahra Davoodi 2*, Farahnaz Bidari 3, Amin Momeni Moghaddam 4, Davood Khalili 1, Hoaman Bahrami-Motlagh 5, Elena Jamali 6, Shahram Alamdari 6, Farhad Hosseinpanah 6, Mehdi Hedayati 7 and Majid Valizadeh 6

Abstract

Background: Regarding the inconclusive results of previous investigations, this study aimed to determine the association between pathology, as a possible predictor, with remission outcomes, to know the role of pathology in the personalized decision making in acromegaly patients.

Methods: A retrospective cohort study was performed on the consecutive surgeries for growth hormone (GH) producing pituitary adenomas from February 2015 to January 2021. Seventy-one patients were assessed for granulation patterns and prolactin co-expression as dual staining adenomas. The role of pathology and some other
CUSHING’S SYNDROME (DISEASE)

- Incidence of 1.6 cases per 1 million persons, 82 are typically small (approximately 6 mm in diameter) and are 5 to 10 times as common in women as in men.

- Micro > Macro

- Corticotroph adenomas account for approximately 70% of cases of Cushing’s syndrome.
<table>
<thead>
<tr>
<th>Findings</th>
<th>% of Patients</th>
<th>Discriminant Index</th>
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<tbody>
<tr>
<td><strong>Symptoms</strong></td>
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<tr>
<td>Weight gain</td>
<td>91</td>
<td></td>
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<tr>
<td>Menstrual irregularity</td>
<td>84</td>
<td>1.6</td>
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<tr>
<td>Hirsutism</td>
<td>81</td>
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<td>Psychiatric dysfunction</td>
<td>62</td>
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<td>Backache</td>
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<tr>
<td>Muscle weakness</td>
<td>29</td>
<td>8.0</td>
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<tr>
<td>Fractures</td>
<td>19</td>
<td></td>
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<tr>
<td>Loss of scalp hair</td>
<td>13</td>
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<tr>
<td><strong>Signs</strong></td>
<td></td>
<td></td>
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<tr>
<td>Obesity</td>
<td>97</td>
<td>1.6</td>
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<tr>
<td>Truncal</td>
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<td>Generalized</td>
<td>55</td>
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<tr>
<td>Plethora</td>
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<td>3.0</td>
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<td>Moon facies</td>
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<tr>
<td>Hypertension</td>
<td>74</td>
<td>4.4</td>
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<td>Bruising</td>
<td>62</td>
<td>10.3</td>
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<td>Red-purple striae</td>
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<td>Muscle weakness</td>
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<td>Ankle edema</td>
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<td>Pigmentation</td>
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<td><strong>Other Findings</strong></td>
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<td>Diabetes</td>
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<td>Overt</td>
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<td>Impaired glucose tolerance test</td>
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<td>ACTH-Dependent Causes</td>
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<td>--------------------------------------------------------------------------------------</td>
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<td>Cushing disease (pituitary-dependent)</td>
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<tr>
<td>Ectopic ACTH syndrome</td>
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<td>Ectopic CRH syndrome</td>
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<tr>
<td>Macronodular adrenal hyperplasia</td>
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<tr>
<td>Iatrogenic (treatment with 1-24 ACTH)</td>
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</table>

<table>
<thead>
<tr>
<th>ACTH-Independent Causes</th>
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<tr>
<td>Adrenal adenoma and carcinoma</td>
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<td>Primary pigmented nodular adrenal hyperplasia and Carney syndrome. McCune-Albright syndrome</td>
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<tr>
<td>Aberrant receptor expression (gastric inhibitory polypeptide, interleukin-1β)</td>
</tr>
<tr>
<td>Iatrogenic (e.g., pharmacologic doses of prednisolone, dexamethasone)</td>
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<table>
<thead>
<tr>
<th>Other Causes of Hypercortisolism</th>
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<tr>
<td>Alcoholism</td>
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<td>Depression</td>
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<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Tumor Type</td>
</tr>
<tr>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Small cell lung carcinoma</td>
</tr>
<tr>
<td>Non–small cell lung carcinoma</td>
</tr>
<tr>
<td>Pancreatic tumors (including carcinoids)</td>
</tr>
<tr>
<td>Thymic tumors (including carcinoids)</td>
</tr>
<tr>
<td>Lung carcinoids</td>
</tr>
<tr>
<td>Other carcinoids</td>
</tr>
<tr>
<td>Medullary carcinoma of thyroid</td>
</tr>
<tr>
<td>Pheochromocytoma and related tumors</td>
</tr>
<tr>
<td>Rare carcinomas of prostate, breast, ovary, gallbladder, colon</td>
</tr>
<tr>
<td>TABLE 15-14</td>
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<tr>
<td>--------------</td>
</tr>
</tbody>
</table>
| **Diagnosis—Does the Patient Have Cushing Syndrome?** | Late night salivary cortisol/circadian rhythm of plasma cortisol  
Urinary free cortisol excretion*  
Low-dose dexamethasone suppression test* |
| **Differential Diagnosis—What Is the Cause of the Cushing Syndrome?** | Plasma ACTH  
Plasma potassium, bicarbonate  
High-dose dexamethasone suppression test  
Corticotropin-releasing hormone  
Inferior petrosal sinus sampling  
CT, MRI scanning of pituitary, adrenals  
Scintigraphy  
Tumor markers |
Cushing syndrome suspected (consider endocrinologist consultation)

Exclude exogenous glucocorticoid exposure

Perform one of the following tests

- 24-h UFC (≥2 tests)
- Overnight 1-mg DST cortisol (≥2 tests)

Consider caveats for each test (see text)
Use 48-h, 2-mg DST in certain populations (see text)

ANY ABNORMAL RESULT

Exclude physiologic causes of hypercortisolism

Consult endocrinologist

Perform 1 or 2 other studies shown above
- Suggest repeating the abnormal study
- Suggest Dex-CRH or midnight serum cortisol in certain populations (see text)

Discrepant (Suggest additional evaluation)
ABNORMAL
Normal (CS unlikely)

Cushing syndrome

Figure 15-20 Algorithm for testing patients with suspected Cushing syndrome (CS) according to the 2008 Endocrine Society's clinical practice guideline. All statements are based on expert opinion and there is no direct evidence available from clinical trials.
PHYSIOLOGIC HYPERCORTISOLISM

May have some clinical features of CS

- Pregnancy
- Patients with severe obesity, especially those with visceral obesity or PCOS
- Patients with psychological stress, especially patients with a severe major depressive disorder and melancholic symptoms
- Poorly controlled diabetes mellitus
- Rarely, chronic alcoholism
- Physical stress (illness, hospitalization/surgery, pain)
- Obstructive sleep apnea

Unlikely to have clinical features of CS

- Malnutrition, anorexia nervosa
- Intense chronic exercise
- Hypothalamic amenorrhea
- High corticosteroid-binding globulin (CBG) (increased serum cortisol but not UFC)
- Glucocorticoid resistance
NONFUNCTIONING PITUITARY TUMORS

• Approximately 25% to 35% of pituitary tumors

• Clinically silent (i.e., do not actively secrete hormones), but they arise from pituitary cells capable of expressing hormone genes, including LH and FSH, and more rarely, ACTH and TSH

• Diagnostic markers useful for determining pituitary tumor classification and behavior:
  • Hormone immunohistochemistry
  • Cell-specific transcription factors to define differentiated cell types proliferative indices.

• Gonadotroph and corticotroph cell tumors predominate amongst the nonfunctioning tumors.

• Presentation:
  • Size
  • Incidentaloma
  • Hormonal hyposcretion
FIG. 1. Flow diagram for the evaluation and treatment of pituitary incidentalomas. a, Baseline.
EVALUATION OF SELLAR MASS (1):

- Should be evaluated both radiologically and hormonally. (Clinically - Visual field)

  **Pituitary Function Tests:**
  
  - Basal level: Prolactin, GH-IGF1, ACTH-Cortisol, FSH-LH-Testosterone (In female with irregular mese: FSH-LH-Estradiol)
  
  - Special tests: Prolactin (PEG/Dilution) - Cortisol (Stimulation: Cosyntropin/ Suppression: ODST)
Fig. 9.29 Management of nonfunctioning pituitary adenomas. Skilled magnetic resonance imaging (MRI) interpretation is crucial to diagnose nonadenomatous mass (e.g., meningioma, aneurysm, or other sellar lesion).
EVALUATION OF SELULAR MASS (2):

• Certain MRI findings: suggest a greater likelihood of some kinds of sellar masses

  As an example, a mass that is separate from the pituitary gland generally indicates that the mass is not a pituitary adenoma.

➢ However, no finding is usually pathognomonic of any one kind of mass
HOW DISTINGUISH DIFFERENT PATHOLOGY?

➢ Why: Correct preoperative diagnosis is clinically important because the treatment of choice for many of these nonpituitary sellar masses differs from that of a pituitary tumor. (Germ cell tumors, Sarcoidosis, LCH, Lymphoma)

• In some cases, there are no features that clearly distinguish the unusual etiologies from the clinically nonfunctioning pituitary adenoma.

• In others, certain endocrine, neurologic, and radiographic findings that are more characteristic of patients with a nonpituitary sellar mass may be present and can help in their differentiation.
SIGNS AND SYMPTOMS OF NONPITUITARY SELLAR LESIONS

- **Clinical DI** at presentation is highly suggestive of a nonpituitary etiology of a sellar or parasellar mass. Sarcoidosis and metastatic disease to the sellar region are especially likely to lead to diabetes insipidus.

- The **(SIADH) syndrome** of inappropriate antidiuretic hormone secretion leading to potentially severe hyponatremia may also occur in patients with nonpituitary sellar and parasellar lesions.
SIGNS AND SYMPTOMS OF NONPITUITARY SELlar LESIONS

• Hypothalamic tumors in children may produce the diencephalic syndrome manifest as wasting, poor development, and sexual immaturity.

• Hypothalamic dysfunction in adults may lead to disruption of the control of appetite and cause syndromes of polyphagia and massive obesity or severe starvation.
MRI:

**Unenhanced image** The normal anterior pituitary gland demonstrates a signal intensity similar to or slightly greater than white matter, whereas the posterior pituitary gland appears bright in most patients owing to the presence of phospholipid within the neurosecretory granules. This bright spot may not be seen in 10% to 20% of normal individuals.

Pituitary adenomas, by contrast, are most often hypointense relative to the normal gland on T1-weighted images, and approximately one third to one half are hyperintense on T2-weighted images.

In delayed images, this pattern may be reversed.

Pituitary adenomas may be confined to the sella, extend suprasellarly toward the optic the lack of sellar enlargement is helpful in diagnosis, which is suggestive for a nonpituitary lesion.
GADOLINIUM-ENHANCED IMAGE

• Normal pituitary tissue takes up gadolinium to a greater degree than CNS tissue and therefore has a higher-intensity signal than the surrounding CNS. Both micro- and macroadenomas of the pituitary (as well as other sellar masses such as craniopharyngiomas and meningiomas) usually take up gadolinium to a lesser degree than the normal pituitary but more than the CNS.

• Therefore, the degree of gadolinium enhancement does not distinguish one kind of sellar mass from another. The postcontrast enhancement of meningiomas is usually homogeneous.

• If a sellar lesion can be seen as separate from the normal pituitary, whether on unenhanced or, more commonly, enhanced images, the lesion is not a pituitary adenoma.
SOME LESIONS:

**Cystic lesions**, such as Rathke's cleft cysts:

- On T1-weighted images low-intensity signal; however, craniopharyngiomas and even pituitary adenomas may be partially cystic and, therefore, have low-intensity signals. Furthermore, the signal intensity on T1-weighted images will be high if the protein or lipid concentration of the cyst fluid is high.
- On T2-weighted images, cystic lesions may have a high-intensity signal.

**Hemorrhage** into the pituitary gland results in a high-intensity signal on both T1- and T2-weighted images.

**Meningiomas** typically have a brighter and more homogeneous signal than pituitary adenomas. They also have a suprasellar rather than a sellar epicenter and a dural-based attachment best seen after contrast enhancement.
Calcification in a craniopharyngioma or meningioma is seen better by CT scan than by MRI.
VISUAL LOSS

• The particular visual field loss may provide some clue as to the nature of the lesion.
  • **Unilateral visual loss**: Lesions anterior to the chiasm, such as meningiomas of the optic nerve sheath
  • **Homonymous hemianopsias**: Lesions compressing the visual system more posteriorly along the optic tract, such as meningiomas or aneurysms.
  • **Bitemporal field cuts** of the classic superior chiasmal compression variety.
  • **More unusual visual deficits**: Lesions involving the chiasm, such as gliomas
  • **Cranial neuropathy**: Nonpituitary masses more commonly originate from or infiltrate parasellar structures
VISUAL LOSS PATTERN:

- Unilateral visual loss
- Homonymous hemianopsias
- Bitemporal field cuts
- More unusual visual deficits
TAKE HOME MESSAGE:
EVALUATION OF SELLA MASS:

- Notice for symptoms and signs of secretory adenoma
  - Prolactinoma: Female/Male
  - Acromegaly: acral enlargement, Headache and …
  - Cushing’s disease: Weight gain, Central obesity , Striae , …. 
- Also symptoms and signs of Hormone deficiency for management targets.
HORMONAL EVALUATION

- **Hormonal hyposcretion** — Usually has no value in the differential diagnosis of a sellar mass. (should be evaluated in all patients in order to identify and replace hormone deficiencies).

  Can be caused by any hypothalamic or pituitary lesion

- One exception to this statement is that the spontaneous development of central DI indicates that the lesion affects the hypothalamus or the stalk and is therefore **not a pituitary lesion**.

- Imaging characteristics
THANK YOU FOR YOUR ATTENTION
STALK LESIONS
A 58-year-old woman sees her oncologist to address a 6-month history of daily headache. Her medical history includes treatment of estrogen-receptor positive breast cancer 4 years ago. She had clear surgical margins and negative nodes at the time of surgery. She was treated with both radiation and chemotherapy. Anastrozole, 1 mg daily, was prescribed, and she still takes this medication. There has been no evidence of recurrence, and mammography of the contralateral breast has been normal.

In the past several months, she has begun to experience vague, general headaches that occur at random times. She has no history of headaches, and because they have become more frequent, she has sought advice from her oncologist. She has no evidence of polyuria, polydipsia, or nocturia. She has no history of changes in her ring or shoe size. Physical examination findings are unremarkable. There is no evidence of altered visual fields, hyperpigmentation, skin tags, striae, ecchymosis, or galactorrhea.

Laboratory evaluation reveals a normal chemistry panel, including a normal blood glucose concentration (fasting) and complete blood cell count. The oncologist orders brain MRI (see image). Because of the observed abnormality (arrow), she is sent to you for further evaluation.

You confirm the patient's history, review of systems, and physical examination findings.

**Dysfunction of which of the following pituitary hormones would be most likely to develop in the near term?**

A. TSH  
B. Antidiuretic hormone  
C. ACTH  
D. GH  
E. Prolactin
ANATOMY

• The normal pituitary stalk is widest superiorly and tapers inferiorly.

• near the median eminence: 3.5 mm,

• at its midpoint: 2.88 mm,

• at its insertion at the pituitary: 1.9 mm

➢ Enlargement of the pituitary stalk greater than 2–3 mm in MRI is pathologic

• On MRI:
  • T1-weighted images, the signal intensity of the stalk is less than that of the optic chiasm and neurohypophysis.
  • Deviation or tilt of the pituitary stalk can be seen without any underlying abnormality
PITUITARY STALK:
PITUITARY STALK:

• Within the pituitary stalk are the axons carrying vasopressin and oxytocin

• Within the stalk are the pituitary portal vessels that transport the various releasing and inhibiting factors collected in the venous plexus of the median eminence to the pituitary sinusoids

• As a consequence of this critical position of the pituitary stalk, patients who develop pathology involving the stalk commonly present with varying degrees of hypopituitarism, diabetes insipidus, and hyperprolactinemia.
PITUITARY STALK LESIONS

Discovered on MRI:
• incidentally
• to investigate symptoms such as DI

Classification:
• Congenital and developmental
• Inflammatory and infectious
• Neoplastic
CONGENITAL LESIONS

**pituitary hypoplasia:**
- Clinically, patients present with short stature because of GH deficiency
- On MRI, these patients can have a hypoplastic, absent, or a short, thickened stalk and an ectopic posterior pituitary
SEPTOOPTIC DYSPLASIA

midline forebrain abnormalities, optic nerve hypoplasia, and hypopituitarism.

On an MRI of a patient with septo-optic dysplasia, one may see lack of an infundibulum, anterior pituitary hypoplasia, and an ectopic or undescended posterior pituitary.

Clinically, GH deficiency is seen first, mutation in the pituitary transcription factor HESX1
DUPLICATION OF THE PITUITARY

These cases are often associated with midline facial abnormalities and many of these patients die in infancy.
**INFLAMMATORY AND INFECTIOUS LESIONS**

- **Infundibuloneurohypophysitis (LINH)**

  The inflammation is limited to the infundibulum and posterior lobe, the term lymphocytic infundibuloneurohypophysitis (LINH)

  **the most common** inflammatory cause of pituitary stalk abnormalities

  **MRI**: thickening of the pituitary stalk, loss of the tapering at the pituitary insertion, and marked enhancement with gadolinium, the normal enhancement of the neurohypophysis is absent on MRI, and clinically DI is present
INFUNDIBULONEUROHYPOPHYSITIS (LINH):

• If the adenohypophysis (infundibulopanhypophysitis) is also involved, anterior pituitary deficiencies can occur.

• Corticotropin (ACTH) is the most common anterior pituitary hormone affected, followed by thyrotropin, gonadotropins, and prolactin.

• **Pathology:** Lymphocytic Infiltration

  • In LINH, the inflammation can be self limited and regression of the lesion can be seen on follow up imaging. DI, however, tends to be permanent.

  • In contrast to lymphocytic hypophysitis: a male predominance and the mean age of occurrence is 47 years.

• The diagnosis of LINH is made based upon clinical, laboratory, and imaging findings; however, a definitive diagnosis can only be made with biopsy.
LINH TREATMENT:

• Glucocorticoids can be used to treat LINH.

• The response to glucocorticoids was more pronounced in those with disease duration < 6 months.

• Improvement in MRI findings occurred in the majority of patients within 6 weeks to 6 months of treatment.
LANGERHANS CELL HISTIOCYTOSIS (LCH)

- Involves the skin, bones, orbit, lungs, and CNS
- Granulomas are formed from a proliferation of histiocytes
- **MRI**: asymmetrically thickened pituitary stalk or a hypothalamic
- Mass that is isointense on T1 images, hyperintense on T2 images, and enhances with gadolinium
- Loss of posterior pituitary enhancement
DIAGNOSIS AND TREATMENT

• Search for extracranial manifestations of LCH with a radiographic skeletal survey, skull series, chest radiograph, and bone scan so that these lesions can be Biopsied.

• Local radiotherapy (1000–2500 cGy) alone or with chemotherapy (etoposide, vinblastine, and/or cyclosporine).
Neurosarcoidosis 5-15% - Usually in context of widespread disease

DI occurs in 25% of patients with CNS sarcoid.

**MRI:** pituitary stalk thickening and enhancement as well as pituitary enlargement. Periventricular lesions and leptomeningeal enhancement can be seen in sarcoidosis and this can help distinguish it from lymphocytic hypophysitis.

A chest radiograph, (CSF) angiotensin converting enzyme (ACE),
**WEGENER’S GRANULOMATOSIS**

- Systemic vasculitis that causes necrotizing granulomas in the upper and lower respiratory tracts and kidneys.
- Mean age of onset is 40 and there is a 2:1 male to female.
- Involvement of the pituitary can occur:
  - via direct extension from nasal, paranasal, or orbital disease,
  - from remote granulomatous involvement
  - from vasculitis of the hypothalamus

Clinically, patients most frequently have DI but hyperprolactinemia and panhypopituitarism have also been reported.
**WEGENER’S GRANULOMATOSIS**

**MRI:** an enlarged pituitary with homogenous enhancement as well as thickening and enhancement of the pituitary stalk, and enhancement of the optic chiasm

Wegener’s granulomatosis can be treated with glucocorticoids and/or cyclophosphamide.
CRANIOPHARYNGIOMA

have a bimodal peak of incidence:
- occurring predominantly in children between the ages of 5 and 10 years,
- second smaller peak in incidence occurs in the sixth decade.
- There is a female preponderance.

Most craniopharyngiomas present as a calcific, cystic suprasellar mass.
CRANIOPHARYNGIOMA

The solid portions typically appear isointense or hypointense on T1-weighted images and hyperintense on T2-weighted images but can also have a mottled appearance owing to calcific regions on MR imaging.

Cystic components demonstrate a high signal on T1-weighted images owing to their high protein content or hemorrhagic components.

Tumoral calcification, which may be best appreciated on CT scan, DI is particularly common and is seen in 70% to 90% of childhood craniopharyngiomas and 40% to 60% of adulthood tumors.
NEOPLASMS

Germinomas typically present as a hypothalamic or pineal mass, however, they can also manifest as isolated pituitary stalk thickening. first two decades of life and both sexes are affected equally.

(hCG) or alpha-fetoprotein (aFP)

The clinical manifestations of suprasellar germinomas: include DI, hypopituitarism, and vision changes
GERMINOMAS

Germinomas progress within 1.3 years of the discovery of pituitary stalk thickening, and within 2.5 years of the diagnosis of DI.

PET scan can be used to assist in making the diagnosis. The PET scan will be positive if the patient has a germ cell tumor, and can help distinguish from processes such as histiocytosis.

Germinomas are highly radiosensitive.

Adjuvant chemotherapy can be given to reduce the radiotherapy doses.
The most common malignancies that result in pituitary metastases are breast and lung cancers. They typically occur in older patients and are often locally invasive and have rapid growth.
PRIMARY TUMORS

that can involve the pituitary stalk include gliomas such as:

- astrocytomas,
- ependymomas,
- and pleomorphic xanthoastrocytomas

Pituicytomas (also called infundibulomas)
INVESTIGATING A PITUITARY STALK LESION

Preliminary investigations:

• Anterior pituitary hormones (FSH, LH, testosterone (men), oestradiol (women), ACTH, cortisol, TSH, fT4, prolactin, GH, IGF-1)
• Full blood examination, blood film, biochemistry, calcium and phosphate, renal and liver function
• Markers of cell turnover (LDH, B2M) and inflammation
  CRP (C-reactive protein), ESR (erythrocyte sedimentation rate)
  Serum ACE, 1,25 dihydroxyvitamin D
• Serum AFP (alpha-fetoprotein) and hCG (human chorionic gonadotropin)
• c-ANCA (cytoplasmic antineutrophil cytoplasmic antibody)

Quantiferon Gold in the presence of risk factors for tuberculosis, such as travel within an endemic area and immunocompromised states.

Urinalysis

• Urine microscopy and culture
• 24 h urine calcium excretion

Imaging

• CT neck, chest, abdomen and pelvis with contrast
Incidental pituitary stalk lesion

clinical review and repeat pituitary hormone testing in 3 months, and MRI pituitary in 6 months, and thereafter every 6–12 months during the first 2–3 years.

If the PS lesion increases significantly in size (>6.5 mm in width) or new lesions develop, or if pituitary hormone deficiency arises or the patient’s clinical status changes, then we suggest proceeding to more invasive investigations including consideration of PS biopsy.

Symptomatic pituitary stalk lesion

Tumour markers of solid organ malignancy

• For selected patients in whom metastatic malignancy is suspected. • e.g. CEA, Ca125, Ca199, PSA.

➢ Serum IgG4

• For patients with features suggestive of IgG4-related hypophysitis, such as autoimmune pancreatitis and chronic sinusitis.

➢ CSF analysis

• CSF analysis for cytology, flow cytometry, immunohistochemistry and polymerase chain reaction (PCR) may be diagnostic in suspected CNS lymphoma and obviate the need for intracranial tissue biopsy.
CSF analysis for microscopy and culture is indicated in patients with risk factors, or clinical or radiographic features suggestive of CNS tuberculosis.

CSF analysis for AFP and hCG should be performed in patients with radiographic features of GCT in whom serum AFP and hCG are negative.

Testicular ultrasonography

Should be performed in men with features of CNS lymphoma to exclude occult testicular lymphoma.

Other imaging modalities

In suspected cases of LCH, radiographic skeletal survey, chest X-ray and whole body bone scan are indicated to assess for extracranial granulomas amenable to biopsy.

Bone marrow aspirate and trephine (BMAT)

For patients with suspected CNS lymphoma as a confirmatory and staging investigation.

Tissue biopsy

Histopathology is required for a diagnosis of metastatic disease from solid organ malignancy, neurosarcoidosis, CNS lymphoma, GCT and LCH.

If peripheral tissue is not available, then PS biopsy should be considered.
1. Isolated PS lesion (especially if width >6.5 mm) with or without associated pituitary pathology on imaging.
2. CDI and/or hypopituitarism, or progressive disease on imaging.
3. Diagnosis unclear from extensive investigations.
4. Alternate tissue sites for biopsy not available or accessible.
5. Pituitary neurosurgical expertise available.
A 68-year-old man with malignant melanoma presents with fatigue, headache, nausea, vomiting, and dizziness. He has had no fever, weight loss, vision symptoms, abdominal pain, diarrhea, or edema. He has a history of nodular malignant melanoma on his back, which was resected 2 years ago, with subsequent development of pulmonary metastases. His medical history also includes hypertension and primary hypothyroidism. His medications include hydrochlorothiazide and levothyroxine (50 mcg daily). Three weeks ago, he had just completed 4 cycles of ipilimumab chemotherapy (monoclonal antibody used to treat metastatic melanoma).

On physical examination, his blood pressure is 102/64 mm Hg and pulse rate is 78 beats/min. He is afebrile, alert, and fully responsive. There are no evident visual field deficits on confrontation testing. There is no goiter or peripheral edema.

Laboratory tests results:
- Sodium = 133 mEq/L (133 mmol/L)
- Potassium = 4.1 mEq/L (4.1 mmol/L)
- Calcium = 8.8 mg/dL (2.2 mmol/L)
- Creatinine = 1.1 mg/dL (97.2 μmol/L)
- Glucose = 132 mg/dL (7.3 mmol/L)
- Prolactin = 42 ng/mL (1.8 nmol/L)
- IGF-I = 52 ng/mL (6.8 nmol/L)
- TSH = 0.02 mIU/L
- Free T₄ = 0.8 ng/dL (10.3 pmol/L)
- Morning cortisol = 2.8 μg/dL (77.2 nmol/L), rising to a peak cortisol level of 19.0 μg/dL (524.2 nmol/L) after the administration of 250 mcg cosyntropin
- Testosterone = 80 ng/dL (2.8 nmol/L)
- LH = 0.2 mIU/mL (0.2 IU/L)
- FSH = 0.4 mIU/mL (0.4 IU/L)
- Urinary sodium = 32 mEq/L (32 mmol/L)
- Urinary osmolality = 420 mOsm/kg (420 mmol/kg)

Brain MRI shows mild diffuse pituitary enlargement without evidence of compression of the optic apparatus (see image).

Which of the following is the most appropriate next step?
A. Perform transsphenoidal surgery
B. Administer radiation therapy
C. Administer glucocorticoids
D. Decrease the levothyroxine dosage
E.Prescribe cabergoline therapy
A 58-year-old woman sees her oncologist to address a 6-month history of daily headache. Her medical history includes treatment of estrogen-receptor positive breast cancer 4 years ago. She had clear surgical margins and negative nodes at the time of surgery. She was treated with both radiation and chemotherapy. Anastrozole, 1 mg daily, was prescribed, and she still takes this medication. There has been no evidence of recurrence, and mammography of the contralateral breast has been normal.

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B. Antidiuretic hormone
C. ACTH
D. GH
E. Prolactin
TAKE HOME MESSAGE

• Clinical background and history (DH, PMH)
• Imaging characteristics (No specific finding- Separate from pituitary- lack of sellar enlargement)
• Hormonal evaluation (Clinical DI)
• Visual field defect
• Extracranial manifestations
THANKS FOR YOUR ATTENTION
A 31-year-old woman first presented 4 years earlier with amenorrhea and galactorrhea. An 11-mm prolactinoma was identified, and she has since been treated with cabergoline. Her current dosage is 0.5 mg twice weekly. She has regular menses and no galactorrhea. She has recently married and wishes to become pregnant as soon as possible; she is using no contraception.

On physical examination, she appears well. Her height is 64 in (162.6 cm), and weight is 140 lb (63.6 kg) (BMI = 24 kg/m²). Her blood pressure is 105/68 mm Hg. No abnormalities are noted.

Laboratory test results:

- Prolactin = 26 ng/mL (4-30 ng/mL) (SI: 1.13 nmol/L [0.17-1.30 nmol/L])
- β-hCG = 2.1 mIU/mL (<3.0 mIU/mL) (SI: 2.1 mIU/mL [<3.0 IU/L])
Pituitary MRI shows a 5-mm left-sided microadenoma (see image, arrow).
WHICH OF THE FOLLOWING IS THE BEST ADVICE FOR THIS PATIENT?

A. Stop cabergoline now
B. Stop cabergoline once pregnant
C. Switch from cabergoline to bromocriptine once pregnant
D. Reduce the cabergoline dosage to 0.25 mg once weekly
E. Continue cabergoline indefinitely

Correct Answer: B

Learning objective:
Guide the management of microprolactinoma in a woman seeking to become pregnant.
RATIONALE:

This patient has had an excellent clinical, biochemical, and radiologic response to cabergoline (a dopamine agonist) used to treat her prolactinoma. The main question relates to the safety of dopamine agonists during pregnancy and when or if they should be discontinued in women who wish to become pregnant.

The main aims of prolactin-lowering therapy in this patient were to restore pituitary-gonadal function and allow spontaneous ovulation, as well as to shrink her macroadenoma to minimize the consequence of pituitary expansion during pregnancy. Stopping therapy suddenly now (Answer A) would put her at risk for relapse given her visible adenoma on MRI and the fact that her serum prolactin remains at the high end of the normal range on her current cabergoline dosage. While the Endocrine Society clinical practice guideline for the management of prolactinoma suggests that therapy can be withdrawn after 2 years if there has been a response to treatment, this should be done gradually with dosage tapering and monitoring of serum prolactin. This may be an option if the patient accepts that there is a risk of recurrence of hyperprolactinemia. However, even if this were embarked upon, the cabergoline dosage should be gradually reduced to 0.25 mg twice weekly (thus, Answer D is incorrect).
RATIONALE CONTINUED:

Both cabergoline and bromocriptine effectively manage hyperprolactinemia. However, cabergoline is often the drug of first choice because it is more effective than bromocriptine and is better tolerated. While there is more accumulated experience with bromocriptine in pregnancy, both drugs are considered safe. The incidence of miscarriage and congenital malformations associated with each drug is no higher than in the general population. As a result of greater experience, some clinicians may favor the use of bromocriptine to treat prolactin excess when pregnancy is desired, although many would use cabergoline. Regardless, in the setting of a microprolactinoma, there is no requirement to continue dopamine agonist therapy once the patient is pregnant (thus, Answer C is incorrect).
It is unusual for dopamine agonist therapy to be continued throughout pregnancy (Answer E) and it is not warranted in this case. Very rarely, treatment may be resumed during pregnancy if an adenoma expands sufficiently to result in visual field impairment. The chance that an increase in the size of a lactotroph adenoma will be clinically important depends on the size of the adenoma before pregnancy. For a microadenoma such as the one described in this vignette, the risk is very low. One review of 12 studies involving 658 patients with microprolactinomas showed that only 2.7% exhibited a symptomatic increase in adenoma size during pregnancy. The only other circumstance in which continuation of dopamine agonist therapy in pregnancy may be prudent is in women who have macroadenomas that are invasive or abutting the optic chiasm and who have not had prepregnancy debulking surgery or radiotherapy.

Therefore, the best course of action is to advise the patient to stop her cabergoline once pregnant (Answer B). Continuation of therapy until that time ensures ongoing fertility, but the small size and position of her microadenoma (away from the optic chiasm) indicate that ongoing treatment during pregnancy is not justified.
REFERENCE(S):


TUBERCULOSIS:

more frequently in women

MRI: can reveal involvement of the paranasal sinuses or pituitary fossa,

thickening of the pituitary stalk, and adjacent meningeal enhancement.

Tuberculomas are isointense-to-hypointense on T1-weighted images and hyperintense on T2-weighted images.
Pituicytomas (also called infundibulomas) are benign tumors that typically arise from the infundibulum.

in men in the third to fifth decades of life. Clinically, patients present with panhypopituitarism and fatigue.

On MRI, pituicytomas have the same isodensity as normal brain tissue, they enhance homogenously with contrast, and there is absence of the normal T1 hyperintensity of the posterior lobe.

Treatment for pituicytomas is surgical resection.
Leukemia (chronic myelogenous leukemia and acute myelogenous leukemia) and lymphoma
PITUITARY STALK INTERRUPTION SYNDROME

an ectopic posterior pituitary,
a hypoplastic anterior pituitary,
and lack of or significant thinning of the pituitary stalk
Imaging of pituitary adenoma

By: M.haghighimoread, MD.
Identify
pituitary gland
sella turcica

Determine Epicentre
of the lesion
In, above, below or
lateral to the sella

Analyse the lesion
signal, cystic, solid
flow void, calcifications

Differential Diagnosis
The pituitary gland is composed of two anatomically and functionally distinct lobes: the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis). The anterior lobe comprises 75% of volume of the gland.

The hormones produced and secreted by the anterior lobe include growth hormone (GH), adrenocorticotropic hormone (ACTH), prolactin (PRL), thyroid stimulating hormone (TSH), luteinizing hormone (LH), and melanocyte-stimulating hormone (MSH).

The anterior lobe of pituitary is isointense to cortical brain on both T1-weighted and T2-weighted images.
The oxytocin and vasopressin, synthesized in the hypothalamus, are transported along the hypothalamo-hypophyseal tract to the posterior lobe and stored there.

The posterior lobe appears as a bright spot on T1-weighted images. Neurosecretory vesicles are responsible for high signal intensity of the posterior pituitary lobe.

The absence of high signal is often associated with central diabetes insipidus or compressive pituitary gland lesions.
Pituitary gland dimensions

- The dimensions of pituitary glands are highly variable, particularly its height. The gland undergoes dramatic changes in size and shape throughout life. A useful guide to the gland’s height in relation to age is “Elster’s rule” of 6,8,10,12:
  - 6 mm for infants and children,
  - 8 mm in men and postmenopausal women,
  - 10 mm in women of childbearing age
  - 12 mm for women in late pregnancy or postpartum women.
- The pituitary stalk has a normal thickness of 2 mm, and it should not exceed a maximum of 4 mm or the width of the basilar artery.
The radiographic size of sella is not a sensitive indicator of pituitary gland abnormality, as the empty sella may itself lead to enlargement of size. Thus the plain radiographs have been replaced by cross-sectional imaging techniques such as CT scanning and MRI.

CT scan, depicting soft tissue calcification, bony destruction, and surgically relevant bony anatomy.

MRI is the examination of choice for sellar and parasellar pathologies due to its superior soft tissue contrast, multiplanar capability and lack of ionizing radiation. In addition, MRI also provides useful information about the relationship of the gland with adjacent anatomical structures and helps to plan medical or surgical strategy.
MRI Techniques

- MRI techniques in diagnosing pituitary lesions have witnessed a rapid evolution, ranging from noncontrast MRI in late 1980s to contrast-enhanced MRI in mid-1990s. Introduction of dynamic contrast-enhanced MRI has further refined this technique in diagnosing pituitary microadenomas.

- Recently, a variety of advanced MR techniques have been evolved which are particularly helpful in evaluating specific cases. These include 3D volumetric analysis of pituitary volume, high-resolution MR imaging at 3 Tesla (T) for evaluating pituitary stalk, diffusion weighted imaging, MR spectroscopy, magnetization transfer ratio, and intraoperative MRI.
It is not always necessary to give intravenous contrast for detecting pituitary microadenomas as patients with a negative scan generally receive the same symptomatic treatment as patients with a microadenoma (usually these patients are women with symptoms of hyperprolactinemia).

The purpose of the scan is to rule out any large lesions. In possible surgical candidates (for example patients with failed medical therapy or pituitary disease not amenable to medical therapy such as Cushing's disease) it is necessary to give contrast to localize the lesion as accurately as possible.
• On an unenhanced scan, approximately 70% of all pituitary microadenomas can be detected. If you give gadolinium, you can reduce the false-negative rate from 30% to 15%.

• As mentioned earlier, this usually does not affect patient management
Dynamic pituitary MRI

- Initially, precontrast T1- and T2-weighted spin echo coronal and sagittal sections are acquired using a small FOV (20×25 cm), thin slices (3 mm), and high-resolution matrix (256×512). Both the dynamic and routine postcontrast images and delayed scanning after 30-60 minutes may be combined in one study for optimum imaging.
- By definition, pituitary microadenomas are less than 10 mm in diameter and are located in the pituitary gland.
A dose of 0.05 mmol/kg of gadolinium injected intravenously is usually adequate. After a bolus injection of intravenous gadolinium, six consecutive sets of three images are obtained in coronal plane every 10 seconds. The enhancement occurs first in the pituitary stalk, then in the pituitary tuft (the junction point of the stalk and gland), and finally there is centrifugal opacification of the entire anterior lobe. Within 30-60 seconds the entire gland shows homogenous enhancement. The maximum image contrast between the normal pituitary tissue and microadenomas is attained about 30-60 seconds after the bolus injection of the intravenous contrast. Most microadenomas appear as relatively nonenhancing (dark) lesions within an intensely enhancing pituitary gland.

The peak enhancement of the pituitary adenomas occurs at 60-200 seconds, usually after the most marked enhancement of the normal pituitary gland, and persists for a longer duration. Delayed scan (30-60 minutes after contrast injection) may demonstrate a reversal of the image contrast obtained at 30-60 seconds on dynamic scanning. This is because the contrast from the normal pituitary gland fades but diffuses into the microadenoma which stands out as a hyperintense focus.
Indirect signs of pituitary microadenoma

- Sellar floor depression
- Infandibular deviation
- Superior bulging of the gland
By definition, pituitary macroadenomas are adenomas over 10mm in size.
Remodeling of sellar floor (scalloping, erosion, increased size) best seen on CT
In the lateral view the dimensions of sella turcica are 11-16 mm in length and 8-12 mm in depth.
They tend to be soft, solid lesions, often with areas of necrosis or hemorrhage as they get bigger. As they grow, they first expand the sella turcica and then grow upwards. Suprasellar extension with elevation and compression of the optic chiasm. Because they are soft tumors, they usually indent at the diaphragma sellae, giving them a 'snowman' configuration. This is one feature that can help distinguish between a pituitary macroadenoma and a meningioma. Another feature which can help differentiate them is enlargement of the sella turcica - this generally only occurs with pituitary macroadenomas that originate in the sella.
Lymphocytic hypophysitis

- Pregnancy or early post partum
- Symmetric enlargement
- Homogenous appearance
- Intense enhancement
- Stalk thickening
- Loss of posterior pituitary bright spot
- Intact sellar floor
- Dural enhancement adjacent to pituitary mass
Lumina (Gd)-enhanced coronal (A) and sagittal (B) T1 MRI of the sella turcica of a patient with LPH. Narrow arrow...
Thickened stalk

- Lymphocytic hypophysitis
- Germinoma
- Lymphoma
- TB
- Sarcoidosis
- LCH
Magnetization transfer (MT) imaging is a recent advancement in the field of imaging which can be used for preoperative and postoperative assessment of pituitary adenomas in patients with hyperprolactinemia.

In MT imaging, the tissue contrast depends mainly on the concentration of macromolecules, and is quantified by the magnetization transfer ratio (MTR).

In patients with hyperprolactinemia, the MTR of prolactin-secreting adenomas is significantly higher, compared to the MTR value of normal pituitary gland in the controlled group, as a result the prolactin-secreting adenomas having high signal on MT images.

Contrary to this, the nonsecreting adenomas have lower MTR compared to that of normal pituitary gland and demonstrate low signal on MT images.
• Most cases of prolactinomas are treated medically, while nonsecreting adenomas are managed surgically.

• The MT technique can also be used in postoperative assessment and follow-up of patients with pituitary adenomas, especially when classical MRI is negative for residual tumor. Increased MTR values are highly suggestive of persistent adenomatous tissue.

• **DWI**: acute pituitary infarction (DDX: hemorrhage, abcess, hypophisitis)

• **T2 & DWI**: soft and hard adenomas
• MRS: hypothalamic glioma (cho↑, NAA↓)
• Craniopharyngioma, germinoma: lipid↑
• Adenoma: cho↑
• Hamartoma: NAA↓, MI↑
• PET: residual or recurrent tumor
Thank you
Pituitary Adenoma
General aspects of Pathological Classification

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Endocrine pathology Fellowship
Department of Pathology, Shariati Hospital
Tehran University of Medical Sciences
• Pituitary adenomas are benign clonal neuroendocrine proliferations arising from adenohypophysial cells.

• With modern methods of imaging and biochemical analysis of hormonal activity, the most recent data suggest that pituitary adenomas are common, occurring in almost 20% of the general population.

• The majority of these tumors are clinically nonfunctioning tumors that are now recognized to be of gonadotroph differentiation.
• The functional status of a pituitary adenoma is defined by the presence of clinical symptoms, not by immunohistochemistry.

• The use of the term “silent adenoma” should be restricted to lesions that have no evidence of clinical or biochemical abnormality.

• It is critical to obtain comprehensive clinical, biochemical, and radiological information.
DIAGNOSTIC STEPS IN THE ASSESSMENT OF SELLAR LESIONS

• The sellar region is the site of a large number of morphological entities arising from the pituitary gland and other adjacent anatomical structures including meninges, blood vessels, brain and nerves.

• The initial evaluation of a sellar lesion starts on hematoxylin-eosin stained slides, which allow the distinction of primary adenohypophysial pathologies from other sellar entities.
• Once a pituitary lesion is determined to be composed of epithelial cells with neuroendocrine differentiation originating from adenohypophysial cells, several steps should be undertaken.

• First, the lesion must be identified as hyperplasia or adenoma.
• Pituitary adenomas reveal total breakdown of normal acinar architecture on reticulin stain, which distinguishes neoplasia from hyperplasia that retains an acinar reticulin pattern.
• The second step is to identify the cell subpopulation responsible for this proliferation.

• This is usually performed by using immunohistochemistry and/or electron microscopy.
DETAILED CLASSIFICATION OF PITUITARY ADENOMAS
IHC studies:

• Transcription factors:
  - Pit-1, Tpit, SF1, ER, GATA2

• Monoclonal antibodies against pituitary hormones:
  - GH, PRL, TSH, ACTH, FSH, LH, αSU
  - LMWK
  - MIB-1 (Ki67)
  - P53
Pit-1 family groups (GH,PRL,TSH)
Tpit-1 family tumor (ACTH)
SF1 family tumor (Gonadotroph)
GATA2 family tumors (Gonadotroph,TSH)
• CAM5.2,CK18
• CK19
• CK7-CK20
PAS staining
Highlights secretory granules of ACTH, TSH and FSH/LH producing adenomas.
<table>
<thead>
<tr>
<th>Adenoma subtypes</th>
<th>Hormones and transcription factors</th>
<th>CAM5.2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pit-1 (GH/PRL/TSH) family tumors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH-producing adenomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Densely granulated somatotroph adenoma</td>
<td>Pit-1, GH (diffuse), and α-SU</td>
<td>Perinuclear</td>
</tr>
<tr>
<td>Sparsely granulated somatotroph adenoma</td>
<td>Pit-1 and GH (weak)</td>
<td>Perinuclear</td>
</tr>
<tr>
<td>Mammosomatotroph adenoma</td>
<td>Pit-1, ERα, GH, PRL, and α-SU</td>
<td>Variable</td>
</tr>
<tr>
<td>Mixed somatotroph and lactotroph adenomas</td>
<td>Pit-1, ERα, GH, PRL, and α-SU</td>
<td></td>
</tr>
<tr>
<td>GH-producing plurihormonal adenoma</td>
<td>Pit-1, (ERα), (GATA-2), GH, PRL, α-SU, and TSH</td>
<td></td>
</tr>
<tr>
<td>PRL-producing adenomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sparsely granulated lactotroph adenoma</td>
<td>Pit-1, ERα, and PRL (golgi pattern)</td>
<td>Few fibrous bodies</td>
</tr>
<tr>
<td>Densely granulated lactotroph adenoma</td>
<td>Pit-1, ERα, and PRL (diffuse)</td>
<td></td>
</tr>
<tr>
<td>Acidophil stem cell adenomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH-producing adenomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyrotroph adenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monomorphous Pit-1 lineage plurihormonal adenoma</td>
<td>(variable) Pit-1, GATA-2, TSH, and α-SU</td>
<td></td>
</tr>
<tr>
<td>Silent subtype 3 adenoma</td>
<td>Pit-1 (ERα and α-SU) and GH/PRL/TSH (variable)</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Tpit (ACTH) family tumors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Densely granulated corticotroph adenoma</td>
<td>Tpit and ACTH (strong, diffuse)</td>
<td>Strong diffuse</td>
</tr>
<tr>
<td>Sparsely granulated corticotroph adenoma</td>
<td>Tpit and ACTH (weak, variable)</td>
<td>Strong diffuse</td>
</tr>
<tr>
<td>Crooke cell adenoma</td>
<td>Tpit and ACTH (juxtanuclear and peripheral)</td>
<td>Ring-like</td>
</tr>
<tr>
<td><strong>SF-1 (Gonadotroph) family tumors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone active gonadotroph adenoma</td>
<td>SF-1, ERα, GATA-2, α-SU, β-FSH, and β-LH</td>
<td>Usually negative</td>
</tr>
<tr>
<td>Hormone-inactive gonadotroph adenoma</td>
<td>SF-1, ERα, GATA-2, and α-SU (variable)</td>
<td>Usually negative</td>
</tr>
<tr>
<td><strong>Transcription factor and hormone-negative adenoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Null cell adenoma</td>
<td>Negative for transcription factors and hormones</td>
<td>Variable positive</td>
</tr>
<tr>
<td><strong>Polymorphous Plurihormonal adenoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plurihormonal adenoma, NOS</td>
<td>Multiple</td>
<td></td>
</tr>
</tbody>
</table>
GH immunostaining with variable positivity
CAM5.2 staining with many fibrous bodies
Sparsely granulated somatotroph adenoma
SF1 immunostaining
Gonadotroh adenoma
WHAT DOES ATYPICAL ADENOMA MEAN?
THE ROLE OF ELECTRON MICROSCOPY
THE IMPORTANCE OF THE NONTUMOROUS HYPOPHYSIS
NEUROENDOCRINE MIMICS OF PITUITARY ADENOMAS
GH producing pituitary adenoma

Dr. Farahnaz Bidari
Loghman Hakim Hospital
SBMU
GH-secreting adenomas account for approximately 20% of PAs.

Patients have signs and symptoms of gigantism or acromegaly, as well as high serum levels of GH and IGF-I. Somatotroph adenomas (SA) occur in the anterior pituitary, arising from growth hormone-producing cells, often in the lateral wings of the gland. Prolactin co-secretion by the tumor is found in approximately 30%---50% of patients and results in signs and symptoms of hyperprolactinemia.
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<th>Cytokeratin</th>
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<td>GH, a-SU</td>
<td>diffuse</td>
</tr>
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<td>Sparsely granulated somatotroph adenoma</td>
<td>Pit-1</td>
<td>GH</td>
<td>dot-like</td>
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<td>Pit-1, ER</td>
<td>GH, PRL, a-SU</td>
<td>diffuse</td>
</tr>
</tbody>
</table>
It is well known that GH-producing pituitary adenomas may coexpress prolactin (PRL) and, less frequently, thyroid stimulating hormone (TSH) . Production of anterior pituitary hormones in non neoplastic as well as neoplastic cells is controlled by several transcription factors and cofactors. Accumulating evidence supports the hypothesis that normal and adenoma cells expressing GH, PRL, and TSH are regulated by the pituitary-specific transcription factor-1 (Pit-1) and, therefore, belong to the Pit-1 cell lineage.
Subtypes

Histologically, monohormonal GH-producing adenomas are classified in two subtypes, densely granulated (DG) and sparsely granulated (SG), based on the density of secretory granules in the cytoplasm of the adenoma cells.
DG- and SG-type cells have different cytoskeletal features, with or without the formation of fibrous bodies, the hallmark of SG type cells, which are globular aggregations of intermediate filaments as seen on electron micrographs.

In DG type cells, CK (CAM5.2) immunostaining is Perinuclear.
Distribution of CK also varies in **plurihormonal** GH adenomas. These adenomas are histologically subcategorized by **EM** analysis. However, the subtypes are difficult to predict on the basis of the CK pattern alone.
Perinuclear predominant group (P-pre), if more than 70% of the cells had perinuclear CK immunoreactivity.

Perinuclear intermediate group (P-inter), when 30% to 70% of the cells had a dot-like CK pattern.

Adenomas in which more than 70% of the cells had a dot-like CK pattern were classified (DP).

E-cadherin is another antibody that may be helpful in differentiating between them, because there is a loss of expression in sparsely granulated GH-secreting adenomas, but not in those densely granulated.
Densely granulated adenomas were the major subtype in all of the monohormonal and plurihormonal GH adenomas:
70% of GH
89% of GH-PRL
85% of GH-TSH
all of GH-PRL-TSH adenomas.
Clinical difference

There is a growing body of evidence that DGSAs and SGSAs behave differently with SGSAs being larger, more common in younger, female patients, more proliferative (higher MIB1 indices) and with a greater capacity to invade surrounding structures. Some studies have found that SGSAs are more poorly responsive to somatostatin treatment than DGSAs although the extent of the impact of tumor subtype on behaviour is unclear.
Densely granulated
Perinuclear pattern

- Densely granulated adenoma have monotonous cells with moderate acidophilic cytoplasm and PAS positive
  - <30% dot like pattern
  - <5% PRL positive
Sparsely granulated

H&E

PAS-OG

GH

Cam5.2
dot-like pattern

Sparsely granulated adenomas consisting of smaller tumor cells with chromophobuc cytoplasms and eccentric nuclei and occasionally pleomorphism.

GH is heterogeneous and less intense, and cytoplasm may show paranuclear eosinophilic structures called “fibrous bodies” (an accumulation of intermediate filaments and endoplasmic reticulum), better visualized with IHC for cytokeratins 8/18 (CAM5.2)
Mixed densely and sparsely granulated somatotroph adenoma
Intermediate (P-inter)

Both cell types
30% to 70% of the cells had a dot-like CK pattern.
Behaviour is more like densely granulated
Negative pattern
Somatotroph Adenoma With Neuronal Differentiation

A rare but pathologically intriguing subtype of SA, always associated with acromegaly and usually presenting as macroadenoma with or without hypothalamic involvement, shows sparsely granulated GH-producing cells admixed with large atypical ganglion cells. These resemble tumor cells seen in gangliocytomas and represent truly metaplastic tumor cells, as they express a mixture of lineage markers that otherwise are virtually never co-expressed (synaptophysin, neurofilament, cytokeratin and GH).

This is of no known clinical relevance and the mechanisms of trans differentiation remain unexplored.
Somatotroph Adenoma With Neuronal Differentiation
Somatostatin Analogue Effect
On Somatotroph Adenomas

Densely granulated somatotroph adenomas tend to respond better to somatostatin analogue treatment than sparsely granulated tumors. This results in a distinct perivascular hyaline / fibrous reaction. The reaction of somatotroph adenomas to somatostatin analogues is morphologically distinct to that of prolactinomas to dopamine agonists.
Somatostatin Analogue Effect On Somatotroph Adenomas
A large number of GH-secreting adenomas may show secondary immunoreactivity for other pituitary hormones (PRL, FSH, LH or TSH).
Mixed GH- and PRL-secreting adenomas

Mixed GH- and PRL-secreting adenomas account for approximately 6.5% of all Pas. Prolactin co-secretion by the tumor is found in approximately 30%—50% of GH adenoma and results in signs and symptoms of hyperprolactinemia.

Patients with these tumors show signs and symptoms of both acromegaly and hyperprolactinemia.
Mixed GH- and PRL-secreting adenomas

The diagnosis of this group of adenomas requires more complex IHC and ultrastructural analysis, and their differentiation is essential because it has clinical and prognostic implications.

Morphologically, three subtypes may be identified:

1. Mixed adenomas of cells secreting GH and cells secreting PRL.
2. Mammosomatotroph cell adenomas.
3. Acidophilic stem cell adenomas.
Mixed adenomas of cells secreting GH and cells secreting PRL

IHC shows labeling for GH and PRL with various degrees of intensity and distribution. (5% of all Pas)

At the ultrastructural level (EM), two separate cell populations are seen.
Mammosomatotroph cell adenomas

Are rare tumors (1% of all Pas)

Ultrastructural analysis shows a well-differentiated adenoma consisting of a population of monomorphic cells having characteristics of GH- and PRL secreting cells.
Acidophilic stem cell adenomas

Acidophilic stem cell adenomas are very rare and their diagnosis has great clinical importance because they may be confused with prolactinomas once most patients show characteristics of hyperprolactinemia. Histologically they are chromophobic tumors, with focal oncocytic changes in cytoplasms. IHC shows labeling for PRL and, to a lesser extent, for GH in the cytoplasm of the same tumor cells. Electron microscopy is required for the accurate identification of these adenomas, and may reveal megamitochondria responsible for the oncocytic appearance in light microscopy.
Molecular Genetics

- G protein α-subunit
- Somatostatin receptor
- Ghrelin receptor
- Aryl hydrocarbon interacting protein
- Gpr101 Mutations And X-Lag
- Signal Transducer and Activator of Transcription 3
- Micro RNA regulation
- Epigenetic regulation
Tumorigenic mechanisms in somatotroph cells. Several mechanisms increase cAMP production, which is key for somatotroph tumorigenesis. Hormones bind to receptors, including GHRH-R, SSTR, GPR101, and GIPR, on the somatotroph cell membrane and increase the activation of adenyl cyclase through Gsα. The consequent increase in cAMP production leads to the dissociation of the regulatory subunits of PKA from the catalytic subunits, which then translocate to phosphorylate CREB in the nucleus and other targets, leading to increased GH expression and cell proliferation. Gsα activation induced by GNAS mutations also leads to upregulation of the cAMP pathway. In addition, ectopic expression of GIPR may lead to an activated cAMP pathway, and GPR101 is a Gsα-coupled constitutively active receptor that leads to increased cAMP signaling.

AIP, aryl hydrocarbon receptor-interacting protein; ATP, adenosine triphosphate; C, catalytic subunit; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element; GHRH, growth hormone-releasing hormone; GHRH-R, GHRH receptor; GIPR, gastric inhibitory polypeptide receptor; GPR101, G protein-coupled receptor 101; Gsα, G protein stimulatory alpha subunit; GTP, guanine triphosphate; PKA, protein kinase A; R, regulatory subunit; SSTR, somatostatin receptor; ZAC1, zinc finger protein PLAGL1.
GNAS

- Guanine Nucleotide-Binding Protein G(s) Subunit Alpha is one of the earliest mutations to be associated with sporadic somatotroph adenomas was at the GNAS complex locus (15-58% of somatotroph adenomas).

- Gsα mutation leads inhibition of G protein and to constitutive activation of adenylyl cyclase (termed the gsp oncogene) resulting in increased cAMP synthesis.

- This mutation may promote tumorigenesis since cAMP can function as a mitogenic signal.
GNAS

GNAS-mutated tumors are often smaller and less invasive, respond better to SSAs, and are usually densely granulated somatotroph adenomas.

In addition, GNAS-mutated tumors have relatively high expression of dopamine receptor (DRD), which suggests a good response to dopamine agonists.

Somatic mutations in GNAS can result in McCune–Albright syndrome. This syndrome is characterized by polyostotic fibrous dysplasia, skin hyperpigmentation, and autonomous endocrine hyperfunction.
Somatostatin receptor

- Differing expression of the somatostatin receptor between adenoma subtypes has been observed and this pattern can be influenced by somatostatin analogue (SSA) treatment.
- A positive correlation has been observed between SSTR2 expression and reduction in GH after SSA treatment.
- Greater expression of SSTR2 has also been associated with densely granulated adenomas, while SSTR5 was associated with sparsely granulated tumors.
Ghrelin Receptor

Ghrelin, also called “the hunger hormone “is a growth hormone secretagogue that acts on the hypothalamus and pituitary and has been associated with increased cell migration and proliferation in certain cancers.
Mutations in AIP (aryl hydrocarbon interacting protein) are most frequently associated with somatotroph adenomas. They are generally truncations or nonsense mutations leading to loss of function, which has resulted in the classification of AIP as a tumor suppressor gene, although the mechanism by which it functions is not yet known.
Mutation in AIP in somatotroph adenomas is associated with larger tumors and more invasive behaviour and more recurrences.

Furthermore, patients with AIP mutations are relatively resistant to treatment with somatostatin analogues although the mechanism of this resistance remains to be clarified.
Treatment with SSAs leads to and is associated with upregulation of AIP expression. The mechanism for this upregulation is not fully understood, but some authors have proposed that it is ZAC1- (zinc finger regulator of apoptosis and cell cycle arrest) mediated. ZAC1 induces G1 cell cycle arrest and apoptosis.

Low levels of AIP expression have been linked to tumor invasiveness suggesting that patients with AIP mutation require more stringent follow-up.
Gpr101 Mutations And X-Lag

- A study of early childhood onset gigantism with growth hormone hypersecretion found heritable microduplications on chromosome Xq26.3. The condition was termed X-LAG or x-linked acrogigantism.

- Analysis of the expression of the genes encoded in this region in a small number of patients showed that GPR101 mRNA was upregulated by up to 1000-fold.
In a screens of 263 patients with gigantism or acromegaly and 579 patients with acromegaly, the incidence of GPR101 mutation was shown to be 1.1% and 0.69% respectively.

GPR101 encodes an orphan G-protein-coupled receptor that is predicted to bind the stimulatory G protein and regulate activation of adenylyl cyclase, resulted in increased proliferation and growth hormone secretion, along with increased cAMP signalling.
Signal Transducer and Activator of Transcription 3 (STAT3)

is a member of the STAT family, and participates in cellular responses to cytokines and growth factors. Its expression is enhanced in somatotroph adenomas, leading to GH hypersecretion, which in turn promotes STAT3 expression.

In primary human somatotroph adenoma-derived cell cultures, the specific inhibitor S3I-201 can inhibit STAT3 expression, thus decreasing GH transcription and reducing GH secretion.
Micro RNA in Somatotroph Adenomas

- Microarray analysis of somatotroph adenomas and normal pituitary gland showed significant downregulation of miR-34b, miR-326, miR-432, miR-548c-3p, miR-570 and miR-603 in adenomas.
- Among the targets of these miRNAs are high-mobility group A1 (HMGA1), HMGA2 and E2F1, genes whose activation plays a role in pituitary tumorigenesis.
- Overexpression of these miRNAs resulted in reduced growth of pituitary adenoma cell lines.
A number of studies propose an epigenetic mechanism of pituitary somatotroph tumorigenesis.

The expression of the adherens junction component E-cadherin has been shown to be significantly lower in sparsely than densely granulated adenomas and lower levels of E-cadherin correlate with larger tumor size, invasiveness, GH and IGF-1 levels and poor acute response to SSAs.
Syndromic somatotroph adenoma

- MEN1
- MEN4
- Carney complex
- X-LAG syn
- NF1
Lactotroph adenoma (Prolactinoma)

Masoumeh Gharib
Associate Professor of Pathology
Mashhad University of Medical Sciences (MUMS)

October 2021
62-year-old female with a history of pulmonary carcinoma and a suprasellar mass.
DDX:
✓ Prolactinoma
✓ Metastatic carcinoma
✓ Plasmacytoma
Prolactinoma

30–50% of all pituitary adenomas with a higher predilection for women than men. Prolactinomas in women are often detected at younger age and smaller size.
Bitemporal hemianopia
Prolactin

✓ secreted in a circadian fashion, with the highest levels attained during sleep and a nadir occurring between 10 am and noon.

✓ secreted in a pulsatile fashion, the amplitude and frequency of which not only vary throughout the day but are influenced by a variety of physiologic stimuli (e.g., stress, postprandially, exercise)

✓ serum half-life of 26–47 minutes

✓ three specimens should be obtained at 20- to 30-minute intervals.

✓ “big” PRL and macroprolactin (“big, big” PRL): polyethylene glycol extraction and centrifugal ultrafiltration

✓ Hook effect: 1 : 100 dilution
The reference value for serum PRL is 1–25 ng/mL (1–25 μg/L) for women and 1–20 ng/mL (1–20 μg/L) for men.

- Stimulatory effect of estrogen
- During pregnancy
- In nursing mothers
Causes of Hyperprolactinemia

Physiologic
- Sleep, stress, postprandially, pain
- Coitus, pregnancy, nipple stimulation or nursing

Systemic disorders
- Chest wall or thoracic spinal cord lesions
- Primary or secondary hypothyroidism
- Adrenal insufficiency
- Chronic renal failure
- Cirrhosis

Medications
- Psychiatric medications
  - Phenothiazines, haloperidol, thioxanthines, buspirone, olanzapine, risperidone, domperidone, monoamine oxidase inhibitors, fluoxetine, amitriptyline
- Metoclopramide
- Antihypertensives: labetalol, α-methyldopa, reserpine, verapamil
- Antihistamines H2: cimetidine, ranitidine
- Estrogens, oral contraceptives, oral contraceptive withdrawal
- Opiates: heroin, methadone, morphine, apomorphine
- Thyrotroph (TRH)

Prolactin-secreting pituitary tumor: prolactinoma, acromegaly

Macroadenoma (compressing the pituitary stalk)

Macroprolactinemia
- Pressure on or transection of the pituitary stalk, interrupting the transmission of dopamine to D2 receptors on the lactotrophs
  - Surgery, traumatic transection, granulomas, metastases, menigioma, irradiation, histiocytosis X

Ectopic secretion of prolactin by nonpituitary tumors

Idiopathic

Polycystic ovarian disease

Epileptic seizures
Genetic profile

✓ Abnormal expression of growth regulatory molecules, intracellular signal transduction proteins, and cell cycle regulatory molecules
✓ Epigenetic alterations (CDKN2A, RB1, DAPK1, MGMT, CASP8, P14,...)
✓ Altered gene expression
✓ Abnormal microRNA
✓ Abnormal somatic mutations
✓ Loss of chromosome 11
✓ Somatic SDHA mutations
5% of may result from a familial or genetic background such as multiple endocrine neoplasia type 1 (MEN1), Carney complex and familial isolated PAs (FIPAs)
Medical therapy with dopamine agonists: the first-line therapy
Surgical resection

✓ failed medical therapy,

✓ acute onset of visual loss,

✓ or acute tumor complications including apoplexy or cerebrospinal fluid leakage
Macroscopy

✓ Microadenoma: expansile, compressive lesions, soft consistency, reddish-tan, with a pseudocapsule
✓ Macroadenoma: widely invasive, with fibrosis, cystic changes, and calcification
Lactotroph adenoma

psammoma bodies

a pituitary stone: extensive form of psammoma bodies
Sparsely-granulated lactotroph adenomas
Densely-granulated lactotroph adenomas
Acidophilic stem cell adenoma
Cytokeratin: perinuclear small fibrous bodies
Transcription factor Pit-1
Sparsely granulated prolactinomas are the most common subtype. Untreated sparsely granulated adenomas exhibit chromophobic morphology and globular juxtanuclear/ Golgi prolactin (PRL) immunoreactivity.

Densely granulated lactotroph adenomas, which are less common, exhibit acidophilic morphology and diffuse cytoplasmic PRL immunoreactivity.

Acidophil stem cell adenomas are rare, aggressive lactotroph tumors composed of oncocytic cells with large cytoplasmic vacuoles corresponding to giant mitochondria. They are marked by nuclear Pit-1 staining, diffuse PRL, and scant growth hormone (GH) reactivity, and occasional fibrous bodies.
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<td>Acidophil stem-cell adenoma</td>
<td>Pit-1, ER</td>
<td>PRL (diffuse), GH</td>
<td>rare dot-like</td>
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Pituitary carcinoma
Pathological changes of lactotroph adenomas after medical treatment
Pathological changes of lactotroph adenomas after medical treatment
Invasive pituitary adenoma
Prognostic and predictive factors in prolactinomas

- Tumor size
- Proliferative potential of tumors
- Estrogen receptor expression
- Drug resistance
- Gender
Pituitary Adenoma Pathology

Corticotroph Adenoma

ELENA JAMALI, MD
Shahid Beheshti University of Medical Sciences
Corticotroph Adenoma

• Corticotroph adenomas are fourth in frequency (following Gonadotroph, Prolactinoma and GH adenoma)

• Account for 15% of adenoma(1.6 cases per 1 milion)

• The most clinically challenging adenoma type. Because the overwhelming majority of corticotroph adenomas (80%) are microadenomas.

• Most occur in women (30-50 years)

• The most common pituitary adenomas in prepubertal children with a significant male preponderance.
Clinical Presentation

1. Cushing disease

- ACTH production simulates bilateral adrenal hyperplasia with cortisol overproduction
- High level hormonal activity
- Size of adenoma does not correspond to level of serum hormones
- 80% of clinically functioning ACTH adenomas are microadenomas
- Should be distinguished from elevated ACTH from nonpituitary sources
2. Nelson syndrome

- Cushing disease from undetected adenoma
- Postadrenalectomy, loss of glucocorticoid feedback, and accelerated growth of adenoma

Nelson’s syndrome occurs when an ACTH adenoma was present but was either so small as to be missed intraoperatively or the patient could not undergo surgical excision for medical reasons in the first place; in either case, the result is the adenoma not being surgically excised. Second line therapy may include a second attempt at surgical removal, medical management, or radiation therapy, but if all that fails, the negative effects of unremitting hypercortisolism may lead to a third line of therapy, bilateral adrenalectomy. Following removal of both adrenals, the corticotroph pituitary adenoma may then eventually enlarge, possibly due to the removal of the negative feedback of cortisol that had been previously produced by the adrenals.
3. Silent corticotroph adenomas nonfunctional

- ~20% of ACTH adenomas
- No clinical or biochemical evidence of hypercortisolism
- Present with tumor mass effects (headache, visual disturbance, hypopituitarism)
- Almost all silent ACTH are invasive macroadenomas, prone to apoplexy.
MR Findings

- Enhancing lesions
- Microadenomas (85%) midline in pituitary; 10-15% locally Invasive
- Macroadenoma (60%) invasive
Microadenomas less than 4 mm are not demonstrated by imaging procedures, even though there is clinical evidence of adenoma. In addition, histology cannot identify a small subset of tumors due to loss during surgery or sectioning of the tissue specimen.

In Nelson syndrome and silent corticotroph adenoma, Surgery yields usually ample specimen.
Laboratory Tests

Endocrine testing

• *Serum ACTH, cortisol levels*
  Levels do not correlate with adenoma size, unlike prolactinomas

• *Dexamethasone suppression test*
  Adenoma-associated ACTH not suppressible

• *Petrosal sinus catheterization (IPSS)*
  To detect increased ACTH level in draining veins

Other peptides derived from proopiomelanocortin (precursor of ACTH) may be produced:

  β-endorphin, β-LPH, CLIP, MSH
Pituitary adenoma type by transcription factor family

Pituitary transcription factor (PIT1)

Steroidogenic factor (SF1)

TPIT
- Densely granulated ACTH (corticotroph) adenoma
- Sparsely granulated ACTH (corticotroph) adenoma
- Crooke cell adenoma
- Clinically silent ACTH adenoma (either densely granulated, i.e., subtype I, or sparsely granulated, i.e., subtype II)
Histologic Features

3 histological subtypes all driven by Tpit:

- Densely granulated ACTH adenomas
- Sparsely granulated ACTH adenomas
- Crooke cell adenoma (least common)
Densely granulated ACTH adenomas

- Sheets of Basophilic monotonous round cells, often arranged around blood vessels.
- Abundant, PAS-positive cytoplasm and strong diffuse immunoreactivity for ACTH
- Abundant keratin filaments
Densely granulated ACTH adenomas
Sparsely granulated ACTH adenomas

- Chromophobic to weakly PAS positive, and demonstrate weaker, more focal ACTH positivity
- Fewer keratin filaments
Sparsely granulated ACTH adenomas
Crooke cell adenoma

Rare variant in which tumor cells show Crooke hyaline changes.

- Crooke's hyaline change in non-neoplastic corticotroph cells:
The physiological response of normal corticotrophs to exposure of excess cortisol (of any source, neoplastic or iatrogenic) is downregulation of ACTH synthesis and development of hyaline, cytokeratin-rich perinuclear rings: Crooke's hyaline degeneration (named after the English endocrinologist Arthur Carleton Crooke).
Crooke cell adenoma

- Crooke’s cell change is seen in the tumour cells
- Tends to be more aggressive than the usual corticotroph adenomas
Crooke cell adenoma

- Tumor cells are large and have a homogeneous glassy, slightly acidophilic cytoplasm with granular basophilia limited to the cell periphery and juxtanuclear region.
- Nuclei may be highly atypical.
- Dispersal of secretory granules and hence ACTH immunostaining to the peripheral submembrane region or displaces them internally next to the nucleus.
- Ring-like accumulation of keratin filaments in CAM5.2 immunostaining
Crooke cell adenoma

In the largest study to date of 36 cases:

- Only 65% of patients with Crooke cell adenomas manifested Cushing disease (the remainder being silent variants);

- 81% were macroadenomas and 72% were invasive.

- All were surgically treated but 60% of patients experienced recurrences, 24% had multiple recurrences, and 12% died;

- Two examples evolved to pituitary carcinoma
Histologic features

**Nelson syndrome**
- Histological features like Cushing adenoma
- Variable mitotic activity
- No Crooke change in normal pituitary

**Silent corticotroph adenoma**
- Variable amphophilia
- Occasional cytologic atypia and variable mitotic activity
- No Crooke change in adjacent normal pituitary
- Silent corticotroph adenoma may be any of 3 histological subtypes
  - **Subtype 1**: Densely granulated corticotroph adenoma
  - **Subtype 2**: Sparsely granulated corticotroph adenoma
  - Crooke cell adenoma
Immunohistochemistry

- **ACTH and β-endorphin (+); Tpit(+)**
  - ACTH diffuse, strong in densely granulated; focal, weak in sparsely granulated

- **CAM5.2 (+);** extensive, present in circular bundles surrounding nucleus in Crooke cell adenoma

- **CK7** is either negative or reactive in only few scattered cells in 90% of all adenoma subtypes; not useful in adenoma identification.

- **CK20 (+)** in most densely granulated ACTH adenomas and nontumorous Crooke cells; *Do not mistake CK20 IHC(+) pituitary adenoma for metastatic tumor.*

- **Ki-67** labeling index
  - Low in Cushing adenomas
  - May be increased in Nelson, Crooke cell, and silent adenomas but not invariably.
ACTH Cell Hyperplasia

• Uncommon cause of Cushing syndrome

• Secondary to corticotropin-releasing hormone secretion from hypothalamic hamartoma or neuroendocrine tumors

• ACTH cell hyperplasia due to hypocortisolism in Addison disease

• Defined as a distention of normal adenohypophyseal acini by a homogeneous population of corticotrophs that does not lead to complete breakdown of the acinar reticulin border.
ACTH Cell Hyperplasia
Many PAs are invasive and unresectable or in some cases of Cushing’s disease, because the tumors themselves are too small to be detected or completely removed during surgery, drugs and stereotactic radiosurgery are needed to achieve tumor control or biochemical remission.

Understanding of the molecular biological characteristics of different types of PA is important.
Recurrence occurs in approximately 10% of these patients after surgical treatment.

60–75% of patients are insensitive to pituitary-targeted drugs (cabergoline and pasireotide).

Understanding of the molecular characteristics of these tumors is necessary to identify additional drug targets.
Syndromic Pituitary Adenoma-Related

- **Multiple Endocrine Neoplasia Type 1 Syndrome**
  Germline mutations in MEN1

- **DICER1 Syndrome**
  Germline mutations in DICER1 gene

- **Lynch Syndrome**
  Germline mutations in MLH1 and MSH2
Molecular Genetics

• ACTH-producing adenomas causing Cushing’s disease are associated with both an excess of corticotroph releasing hormone (CRH) and a loss of negative feedback inhibition by glucocorticoids.

• However, no mutations in either the CRH receptor or the glucocorticoid receptor have been reported.
Genetic Mutations

- **USP8**
  Ubiquitin-specific protease that regulates the fate of numerous cellular proteins

- **USP48 and BRAF**

- **Somatostatin Receptors**

- **Cyclins And Cyclin-Dependent Kinases**

- **Heat Shock Protein 90**
  Overexpressed; **Silibinin**, HSP90 inhibitor, reported to have anti-tumorigenic effects.
USP8 (Ubiquitin-Specific Peptidase 8)

- Upto 62.4% of corticotropin-secreting adenomas have USP8 mutation.
- USP8 encodes a deubiquitinase enzyme that protects EGFR from degradation.

*Mutation leads to increased activity of USP8*

*Activation of EGFR signaling*

*leads to the synthesis and secretion of adrenocorticotropic hormone (ACTH) and promotes tumorigenesis*
Tumorigenic mechanisms in corticotroph cells
Mutations in USP8 were found to be:

- More common in **adult** than pediatric cases
- More common in **females** than males (ratio 5:2)
- Associated with **earlier onset**
- Patients with a USP8 mutation were less likely to develop postoperative adrenal insufficiency.
- Tumors were found to be **smaller** (*microadenoma*) and to produce more ACTH than their wild-type counterparts.
Potential therapeutic drugs:

✓ **Lapatinib**, an EGFR inhibitor, decreases proliferation in vitro and reduces tumor weight in vivo.

✓ SSTR5 expression is higher in USP8-mutated tumors potentially allowing mutation status to be used as a predictor of response to pasireotide.
USP48 and BRAF

Two mutated genes in mitogen-activated protein kinase (MAPK) pathway
- USP48 mutations: in 23% of corticotropin-secreting adenomas
- BRAF mutations: in 16% of corticotropin-secreting adenomas

Both mutations enhance the promoter activity and transcription of the ACTH precursor, the proopiomelanocortin (POMC) gene, and are potential therapeutic targets for the excess secretion of ACTH.
Somatostatin Receptors

• SSTR1 and 2 was expressed in greater quantities in silent corticotrophs (SSTR2 5-fold increase)
• whereas in Cushing’s disease, SSTR5 was expressed more highly (14-fold increase)

Although the implications of this difference in expression are not fully understood, it may be that treatments that selectively target SSTR5 could be useful for ACTHoma treatment.
CDKN2A expression was four times greater in ACTH-expressing than silent corticotroph adenomas, while cyclins D1, E1 and B1 were suppressed.

It is suggested that the upregulation of a cell-cycle inhibitor combined with the downregulation of cyclins may restrict growth of ACTH-producing adenomas compared to their silent counterparts.
DNA Methylation

• A complementary mechanism for gene mutations, also plays an important role in PAs.

• POMC
  Hypomethylation of the promoter of POMC → Overexpression of POMC

• FGFR2

• Apoptosis-related factors (ESR1 and Caspase 8)
MiRNA Regulation

The tumor suppressors *miR-15a*, *miR-16*, and *miR-132* are downregulated in corticotroph adenomas.

These miRNAs inhibit the proliferation, invasion, and migration of pituitary tumor cells by targeting sex-determining region Y-box 5 (SOX5).
THANKS FOR YOUR ATTENTION!