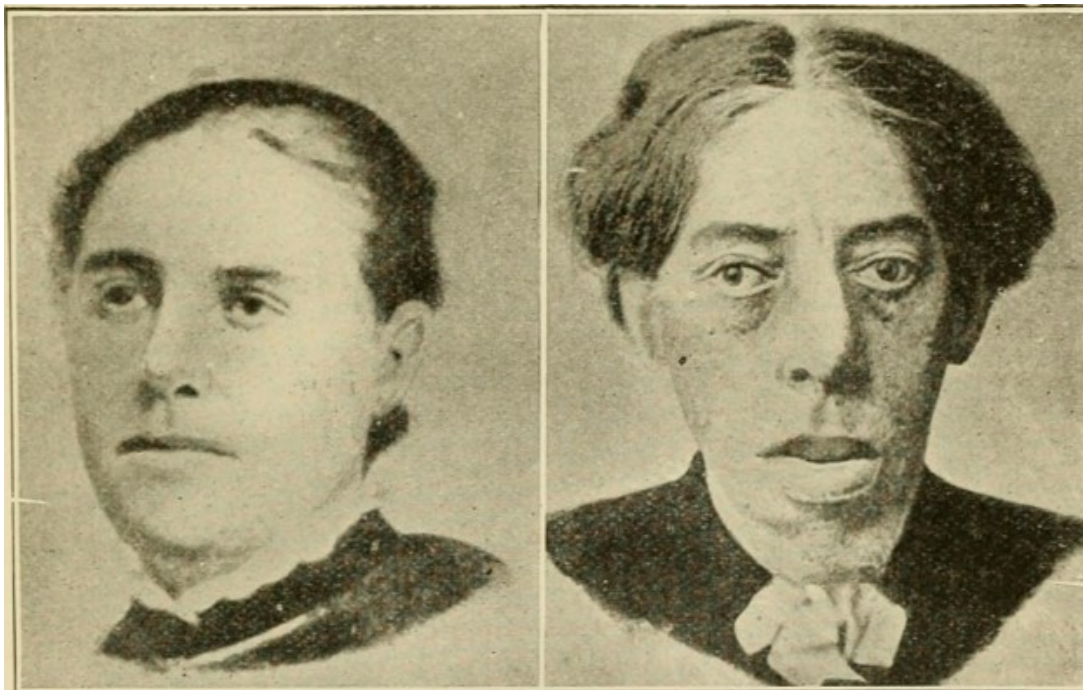


Acromegaly — Symptoms and Treatment

[See online here](#)

Excess production of growth hormone by the pituitary gland in the body is given the name Acromegaly. The exact cause behind Acromegaly can be benign, noncancerous tumors formed in the pituitary gland. Middle-aged adults are more prone to develop acromegaly. It is often diagnosed very late because of its slow and insidious onset. The symptoms vary from swelling of hands and feet to protruded lower jaws, joint pain, and deep voice. Accurate diagnosis is established by an elevated level of growth hormone (GH) and Insulin-like Growth Factor I (IGF-1) in the blood.



Definition and Overview of Acromegaly

Acromegaly - also known as gigantism

Description and synonyms: acromegaly (ancient Greek for “extreme” and “large”), gigantism, Pierre Marie’s disease.

Epidemiology of Acromegaly

In the United States, there are approximately **1,000–2,000** newly diagnosed cases of acromegaly per year. It has a prevalence of approximately 20,000 in the United States.

The median age of diagnosis of this disease is about **40 years**. Since this disease is

marked by a stealthy beginning and course, a lag of 9–10 years between the start of the disease and its diagnosis is common, even with advanced medicine.

No significant differences have been proven regarding the incidence of disease between men and women. Life expectancy is shortened by about 10 years in patients with acromegaly since malignant tumors are common.

Etiology and Pathogenesis of Acromegaly

Growth hormone (GH) in acromegaly

Note: GH = growth hormone = somatotrophic hormone = STH

GH is a peptide hormone which is produced in the adenohypophysis. GH is secreted predominantly during sleep and in puberty. It has an **insulin-antagonistic, growth-stimulating**, and **anabolic** (intracellular integration of amino acids ↑, protein synthesis ↑) effect. GH has no direct effect but commutes via the IGF-1 synthesis in the liver.

Nutrition also affects GH production. It increases with the following:

- Hypoglycemia
- Strain
- Stress
- Physical strain

Note: 1. GH is responsible for the support of cell growth and cell propagation in the locomotor system and connective tissue.

2. GH increases gluconeogenesis in the liver and stimulates glucagon secretion.

Hormonal regulation

- The hypothalamus forms GH-releasing hormone somatoliberin GHRH ⇒ stimulation of GH-formation.
- The hypothalamus forms GH-Inhibiting hormone somatostatin GHIH ⇒ inhibition of GH-formation.
- GH acts in the periphery through the liver-formed **insulin-like growth hormone IGF-1**. The negative feedback mechanism does not function in acromegaly. For more information, read the [Hypothalamus Pituitary Adrenal Axis](#) article.

GH-producing hypophyseal adenoma

In most cases, the overproduction during acromegaly is caused by a **monoclonal pituitary adenoma**. GH-producing tumors make up 20 % of hypophyseal adenomas. In rare cases, acromegaly is caused by a decrease in somatotropin production or an excess of GHRH. An undue secretion of growth hormone leads to an enlargement of **organs** and **extremities** which give the impression of crude facial aspects.

When an overproduction of GH occurs in childhood, where growth plates have not yet fused, it results in **gigantism**. The afflicted are commonly over 6'6" tall. Due to malocclusion and enlargement of the temporomandibular joint, orthodontists and dentists are the primarily consulted specialists.

Symptoms and Clinical Presentation of Acromegaly

Clinical symptoms of acromegaly are the result of elevated stimulation of endochondral and appositional bone growth, elevated stimulation of [skin](#) and skin appendages as well as organ growth.

Children (before growth plate fusion)	Adults (post growth plate fusion)
Hypophyseal gigantism > 6'6"	Acromegaly, visceromegaly

Typical characteristics of acromegaly



Image: "Facial aspect of a patient with acromegaly." by Openi. License: [CC BY 2.0](#)

- **Visceromegaly** (visible organ enlargement, e.g., goiter formation);
- **Enlargement** of osseous **extremities**;



Image: "Hand of a person with acromegaly (B) and a healthy woman (A)" by Openi. License: [CC BY 2.0](#)

- Thickening of the dermis (**pachydermia**): hypesthesia, paresthesia;
- Macroglossia: enlargement of the tongue with dysphonia;

- Enlarged nose;
- Formation of supraorbital bulges;
- Separation of the teeth and broadened **interdental grooves**;
- Headache, fatigue, bone pain, perspiration.

Note: Important anamnestic questions: Does your wedding band still fit? Has your shoe or hat size changed?

Acromegaly – possible complications

- Cessation of the functioning of remaining adenohypophysis – symptoms through encroaching growth.
- Disturbances in the visual field (**bitemporal hemianopsia** due to compression of the chiasma opticum).

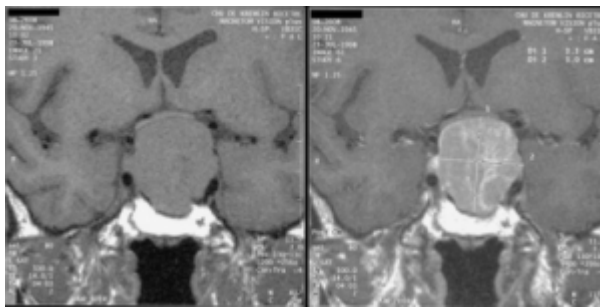


Image: "Pituitary macroadenoma with suprasellar extension, compressing the optic chiasm." by Openi. License: [CC-BY 2.0](https://creativecommons.org/licenses/by/2.0/)

- Carpal tunnel syndrome due to connective tissue hyperplasia.

Secondary complications in acromegaly

- Sleep apnea (> 90 % of patients are affected);
- [Diabetes mellitus](#);
- **Secondary hypogonadism** (women: secondary amenorrhea and menstrual cycle disturbances, men: loss of libido and potency), hyperprolactinemia, erectile dysfunction;
- Hypertension (30 % of patients);
- Spinal column and joint complaints;
- Increased incidence of colon and [breast cancers](#).

An acromegaly case report

The following could be a case report for acromegaly in a board exam:

A 45-year-old male was noted to display the typical changes of acromegaly (**enlargement of the nose, ears, lips, tongue, fingers, and toes**). Endocrinologic diagnostic procedures showed pathologically elevated **growth hormone levels**. A diagnosis of acromegaly was concluded. Following MRI showed a small pituitary tumor with little contrast agent uptake, which hinted at a **growth hormone releasing adenoma**.

The tumor was surgically removed by gaining access via the right nasal cavity and sphenoidal sinus using a surgical microscope and endoscope. Post-operative growth

hormone levels returned to normal levels. A post-surgical MRI showed a complete removal of the adenoma with proper visualization of the normal pituitary gland. Post-operative hormone tests supported the normal functioning of the remaining pituitary gland such that the patient did not require hormone substitutes. The acromegaly was cured with **surgical intervention** alone.

Source: [University of Greifswald](#)

Diagnosis of Acromegaly

Acromegaly should be diagnosed as early as possible.

Note: Early detection can minimize the patient's suffering and consequences! When suspecting acromegaly, ask the patient for an older portrait picture such as an old driver's license and compare facial features.

Laboratory studies

Secretion of GH varies by time of day. Therefore, single observations of GH are not useful for diagnosing acromegaly. The easiest diagnostic medium is the **OGTT** (oral glucose tolerance test) with a parallel observation of **serum GH**. In the presence of acromegaly, a missing suppression of GH < 1 µg/l is typical.

Furthermore, a hormone analysis of **IGF-1** and GH can be useful, which would show pathologically high levels for both. Bound IGF-1 has a serum half-life of up to 18 hrs, which indicates that serum observation is sufficiently meaningful.

For purposes of ruling out further hormone-producing adenomas of the adenohypophysis, testing for LH/FSH, TSH, prolactin, and ACTH are called for. Often complete or partial **hypopituitarism** is observed in parallel.

Pathology

Microscopically, one can differentiate **sparsely-granulated** (aggressive) and **densely-granulated** (less aggressive) tumors. In a third of the cases, there is also an elevated secretion of prolactin (monomorphic, mono-cellular, mixed cell adenomas).

Radiologic procedures

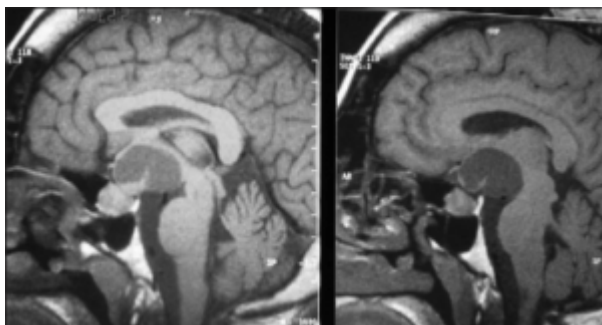


Image: "Pituitary macroadenoma with suprasellar extension, compressing the optic chiasm." by Openi. License: [CC-BY 2.0](#)

Patients with acromegaly will show an enlarged sella turcica on x-ray, the nasal sinuses, and the heart. MRI is well suited for tumor discovery.

Differential Diagnoses of Acromegaly

Similar diseases such as acromegaly

GH-disturbance without adenoma	Hereditary acromegaly	Further differential diagnoses
Pituitary hyperplasia	MEN-1 syndrome	Constitutional tallness
Ectopic/paraneoplastic GH-/GHRH-formation	McCune-Albright syndrome	Acromegaloid
	Familial acromegaly	Hyperostosis generalisata (primary hypertrophic osteoarthropathy, pachydermoperiostosis)
	Carney complex	

Treatment of Acromegaly

Surgical treatment

Trans-sphenoidal adenoidectomy via endo-nasal access is the current standard of care. This surgery is performed because of its curative potential. With complete removal of the tumor, the hormone level decreases immediately.

Note: If GH levels fall below 2 µg/l, the patient can be assumed cured.

Final proof for successful tumor removal with cure of the acromegaly is declared several weeks after the surgery through renewed endocrinologic examination.

Radiation therapy

Inoperable tumors or an incomplete resection can call for stereotactic radiosurgery, proton therapy, and conventional **radiation therapy**. The effect of the radiation, however, is often not immediate but can occur after several years under certain circumstances. Furthermore, one must consider the risk of anterior pituitary insufficiency.

Therapeutic medication

In the case of **inoperability** and transient radiotherapy, pharmacologic treatment is called for. If the patient's tumor is large, preoperative pharmacologic treatment can be useful to induce tumor shrinkage and improve the patient's general constitution. All medication targets the inhibition of GH secretion:

Drug group	Effect	Examples
Dopamine-D2-agonists	Inhibition of GH-production by the pituitary adenoma	Bromocriptine, Cabergoline
GH-receptor-antagonists	Normalization of the elevated IGF-1 level	Pegvisomant
Somatostatin-analogs	Decreased size of the adenoma, normalized GH level	Octreotide, Lanreotide

Prognosis of Acromegaly

Lowered life expectancy for acromegaly patients.

Life expectancy of people with acromegaly is significantly limited due to secondary

complications. **Lethality** is twice as high and up to four times as high as healthy individuals. Main reasons for this are usually hypertension, cardiovascular disease, and diabetes mellitus.

Review Questions

The answers are below the references.

1. Clubbed nails were observed during the routine exam of 48-year-old Mrs. F. Clubbed nails are typical of a host of diseases. Which of the following diseases is most indicated?

1. Pituitary adenoma (e.g., prolactinoma, acromegaly)
2. Mitochondrial diseases (e.g., chronic, progressive ophthalmoplegia)
3. Chronic insufficiency of the adrenal gland cortex (e.g., Addison's disease)
4. Malignant lung disease (e.g., bronchial carcinoma)
5. Chronic renal insufficiency (e.g., diabetic nephropathy, analgesic nephropathy)

2. A 65-year-old female patient complains during consultation about persistent and increasingly worsening pain in her legs and pelvis. She further notes, by-the-by, that her hats have been getting tight, such that some no longer fit. Lab work shows high levels of alkaline phosphatase (ALP) at 550 U/L. You order cranial x-rays and skeletal scintigraphy. Which diagnosis, however, do you suspect already?

1. Metastatic breast cancer
2. Renal osteopathy
3. Ostitis deformans (Paget's disease)
4. Acromegaly
5. Chronic arsenic toxicity

3. Over the past two years, the facial features of a 61-year-old male patient have become increasingly crude and his hands have enlarged. Blood work revealed increased GH levels. Magnetic resonance imaging showed a microadenoma of the pituitary gland. After surgical removal of the adenoma via trans-nasal, trans-sphenoidal access, the soft tissue swelling as well as the high hormone levels observed in the blood reversed completely. MRI showed a complete removal of the hormone-producing microadenoma. If the adenoma had been inoperable, which of the following drug groups could have been called on?

1. Dopamine-D2-agonists
2. Dopamine-antagonists
3. GH-receptor-agonists
4. Somatostatin-antagonists
5. L-Dopa

References

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Correct answers: 1D, 2C, 3A

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Notes