Acromegaly — Symptoms and Treatment

Acromegaly refers to excessive synthesis of growth hormone by the pituitary gland. The etiology of acromegaly is benign and involves noncancerous tumors formed in the pituitary gland. Middle-aged adults are highly prone to develop acromegaly. Its diagnosis is delayed 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 elevated levels of growth hormone (GH) and insulin-like growth factor I (IGF-1) in the blood.

Definition and Overview of Acromegaly

Acromegaly is 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, approx. **1,000-2,000** cases of acromegaly are newly diagnosed each year. Its prevalence in the United States is approx. 20,000.

The median age of diagnosis of acromegaly is about **40 years**. Since this disease is marked by a stealthy beginning and course, a lag of 9-10 years between the onset of the disease and its diagnosis is common, even with advanced medicine.
No significant differences in the incidence of the disease have been found between men and women. Life expectancy is shortened by about 10 years in patients with acromegaly due to malignant tumors.

Etiology and Pathogenesis of Acromegaly

**Growth hormone (GH) in acromegaly**

**Note:** GH = growth hormone = somatotropic hormone = STH

GH is a peptide hormone 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. The effect of GH is indirect and mediated via IGF-1 synthesis in the liver. Nutrition also affects GH production. **Its levels increase in:**

- Hypoglycemia
- Strain
- Stress
- Physical strain

**Note:**
1. GH is responsible for cell growth and mechanical signal propagation in the locomotor system and connective tissue.
2. GH increases gluconeogenesis in the liver and stimulates glucagon secretion.

**Hormonal regulation**

- The hypothalamus produces GH-releasing hormone (also known as somatoliberin) GHRH ⇒ stimulation of GH-formation.
- The hypothalamus synthesizes GH-Inhibiting hormone (somatostatin) GHIH ⇒ inhibition of GH-formation.
- GH acts peripherally via *insulin-like growth hormone IGF-1* generated in the liver. No negative feedback mechanism exists in acromegaly. For more information, read the [Hypothalamus Pituitary Adrenal Axis](#) article.

**GH-producing hypophyseal adenoma**

In most cases, GH overproduction during acromegaly is caused by a *monoclonal pituitary adenoma.* GH-producing tumors constitute 20% of all hypophyseal adenomas. In rare cases, acromegaly is induced by a decrease in somatotropin synthesis or an excess of GHRH. Undue secretion of growth hormone leads to enlarged organs and extremities, underlying the crude facial appearance.

Overproduction of GH in childhood results in gigantism, in the absence of growth plate fusion. The afflicted patients are generally 6’6” tall. The characteristic malocclusion and enlargement of the temporomandibular joint are the domain of orthodontists and dentists, who are the primary consultants specializing in these abnormalities.

**Symptoms and Clinical Presentation of Acromegaly**

Clinical symptoms of acromegaly are attributed to elevated stimulation of endochondral and appositional bone growth, and increased stimulation of skin and skin appendages as
well as organ growth.

<table>
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<tr>
<th>Children (before growth plate fusion)</th>
<th>Adults (post-growth plate fusion)</th>
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<tr>
<td>Hypophyseal gigantism &gt; 6'6&quot;</td>
<td>Acromegaly, visceromegaly</td>
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</table>

**Typical characteristics of acromegaly**

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

- 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 residual adenohypophysis function — overgrowth symptoms
- Visual field disturbances (bitemporal hemianopsia due to compression of optic chiasma)

![Image: Pituitary macroadenoma with suprasellar extension, compressing the optic chiasm. By Openi, License: CC-BY 2.0](image)

- 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

A 45-year-old man presented with the typical changes of acromegaly (enlarged nose, ears, lips, tongue, fingers, and toes). Endocrinology tests showed pathologically elevated growth hormone levels. A diagnosis of acromegaly was concluded. Subsequent MRI showed a small pituitary tumor with little contrast uptake, which suggested a growth hormone-releasing adenoma.

The tumor was surgically removed by gaining access through the right nasal cavity and the sphenoidal sinus using a surgical microscope and endoscope. Post-operative growth hormone levels returned to normal levels. A post-surgical MRI showed complete removal of adenoma with adequate visualization of the normal pituitary gland. Postoperative hormone tests revealed normal functioning of the remaining pituitary gland without the need for hormone replacement. Acromegaly was cured with surgical intervention alone.
Diagnosis of Acromegaly

**Acromegaly should be diagnosed as quickly 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**

The secretion of GH varies by the time of the day. Therefore, single observations of GH are not useful for the diagnosis of acromegaly. The easiest diagnostic test is the **OGTT** (oral glucose tolerance test) with a parallel observation of **serum GH**. In the presence of acromegaly, GH levels are not suppressed to $< 1 \mu g/L$.

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

To exclude further hormone-producing adenomas of the adenohypophysis, patients are tested for LH/FSH, TSH, prolactin, and ACTH. Often complete or partial **hypopituitarism** is observed in parallel.

**Pathology**

Microscopically, the tumors in acromegaly can be differentiated into **sparsely-granulated** (aggressive) and **densely-granulated** (less aggressive) types. In a third of the cases, elevated secretion of prolactin (monomorphic, mono-cellular, mixed cell adenomas) is also observed.

**Radiologic procedures**

![Image: Pituitary macroadenoma with suprasellar extension, compressing the optic chasm. By Openi, License: CC-BY 2.0](image)

Patients with acromegaly show an enlarged sella turcica on skull X-ray, the nasal sinuses, and the heart. MRI is indicated for tumor screening.

**Differential Diagnoses of Acromegaly**
Similar diseases such as acromegaly

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<td>Pituitary hyperplasia</td>
<td>MEN-1 syndrome</td>
<td>Constitutional tallness</td>
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<td>Ectopic/paraneoplastic GH-/GHRH-formation</td>
<td>McCune-Albright syndrome</td>
<td>Acromegaloid</td>
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<td>Familial acromegaly</td>
<td>Primary hypertrophic osteoarthropathy or pachydermoperiostosis</td>
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<td>Carney complex</td>
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Treatment of Acromegaly

Surgical treatment

**Trans-sphenoidal adenoidectomy** via endonasal access is the current standard of care. This surgery is curative, resulting in an immediate decline in hormone levels following complete tumor excision.

**Note:** GH levels declining below 2 µg/L indicate cure.

Final evidence suggesting successful tumor removal and cure in acromegaly is obtained several weeks after the surgery based on a renewed endocrinologic examination.

Radiation therapy

Inoperable tumors or incomplete resection warrant stereotactic radiosurgery, proton therapy, and conventional radiation therapy. The effect of radiation, however, is often not immediate but occurs after several years under specific circumstances. Furthermore, one must consider the risk of anterior pituitary insufficiency.

Therapeutic medication

Pharmacologic intervention is indicated for patients with **inoperable acromegaly** and refractory to transient radiotherapy. If the patient’s tumor is large, preoperative pharmacologic treatment may be useful to induce tumor shrinkage and improve the patient’s general constitution. All medications are targeted at GH secretion to induce inhibition:

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<td><strong>Dopamine-D2-agonists</strong></td>
<td>Inhibition of GH-production by the pituitary adenoma</td>
<td>Bromocriptine, Cabergoline</td>
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<td><strong>GH-receptor-antagonists</strong></td>
<td>Normalization of the elevated IGF-1 level</td>
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<td><strong>Somatostatin-analogs</strong></td>
<td>Decreased size of the adenoma, normalized GH level</td>
<td>Octreotide, Lanreotide</td>
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Prognosis of Acromegaly

**Lowered life expectancy**

The life expectancy of patients with acromegaly is shortened by approx. 10 years due to secondary complications. **Lethality** is twice as high and up to 4-fold as high as healthy
individuals. The primary reasons for decreased life expectancy are usually hypertension, cardiovascular disease, and diabetes mellitus.

References


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