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ABSTRACT

Acromegaly is a rare, progressive disorder characterized by the hypersecretion of growth hormone (GH) and subsequent overproduction of Insulin-like growth factor-1 (IGF-1), typically resulting from a benign pituitary somatotroph adenoma. This chronic exposure leads to coarse facial features, acral enlargement and severe systemic comorbidities involving the cardiovascular, metabolic, and respiratory systems. Without early diagnosis and multidisciplinary treatment, the disease is associated with significantly increased morbidity and mortality. Primary care physicians and specialists may play an important role in early diagnosis and timely treatment. The primary marker for screening is IGF-1 and not GH since the latter has influencing factors causing variations in levels. However, a GH suppression test may be useful in some patients. Surgical, medical and radiation therapies are the main line of treatment in acromegaly. Despite effective treatment, most comorbidities persist or even progress. Survival rates are dictated by geographic factors, health care system, length to diagnosis, length of follow-up, healthcare system. Lower mortality rates are reported in recent years but increased standardized mortality rates due to cardiovascular and oncological causes are still reported in subpopulations with diagnostic delay of more than 10 years. Although multimodal treatment regimens are available, poor adherence to treatment, ineffective treatment, adverse effects or combinations of these act as limiting factors in achievement of treatment goals. Diagnostic delays are likely to be minimized in the coming times owing to improved scoring and AI systems for screening. Better outcomes could be achieved in future through modern surgical techniques, increased access to molecular profiling of tumors, newer and more efficient treatment with better adherence and improved clinical monitoring during follow-up.

INTRODUCTION

Acromegaly most commonly results from hypersecretion of growth hormone (GH) by benign adenoma of somatotrophs in the adult anterior pituitary (in other words, hypersecretion of GH after fusion of epiphyseal plates). Occurrence rate is 1 in a 100000 persons. Although the causes of acromegaly can be categorized as primary GH hypersecretion, ectopic or iatrogenic GH hypersecretion and hypersecretion of GH releasing hormone (GHRH), extra pituitary causes of acromegaly are rare. It is to be noted here that of all pituitary adenomas, 20% are GH secreting and 25% are prolactin secreting (resulting in prolactinomas). Of the GH secreting pituitary adenomas, 95% are with no known genetic causes.

GH hypersecretion of acromegaly results in increased production of Insulin-like growth factor-1 (IGF-1), which causes excess growth of soft tissues resulting in prognathism (prominent jaw), coarse facial features, enlargement of hands and feet, large internal organs and systemic effects including cardiovascular, metabolic, neoplastic, neurologic, pulmonary and

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rheumatologic. Macroadenomas can also cause visual disturbances. Early diagnosis and treatment are imperative to curb associated morbidities and mortalities of acromegaly.

The purpose of this review is to provide a comprehensive update on the current understanding of acromegaly viz. its clinical features, pathogenesis and pathophysiology, diagnosis, treatment, disease course and the general physician's role in early diagnosis and treatment/ management.

ETIOLOGY

The causes of acromegaly can be categorized as primary GH hypersecretion, ectopic or iatrogenic GH hypersecretion and hypersecretion of GH releasing hormone (GHRH).

The most common cause of acromegaly is a GH-secreting adenoma of somatotrophs of the adult anterior pituitary gland. Other causes of primary GH-hypersecretion include pituitary adenomas secreting multiple hormones and carcinomas of GH-secreting cells. Ectopic causes include GH production by lymphomas and pancreatic islet cell tumors. Excess GH-administration is the most common iatrogenic cause. Acromegaly due to hypersecretion of GHRH can be further categorized into central and peripheral causes. Central causes are hypothalamic and include hamartomas, choristomas and ganglioneuromas. Acromegaly-causing peripheral production of GHRH include bronchial carcinoid tumor, small cell lung cancer, adrenal adenoma, medullary thyroid cancer, pheochromocytoma.

Among all pituitary adenomas, 20% are GH secreting and 25% are prolactin secreting (resulting in prolactinomas). Of the GH secreting pituitary adenomas, 95% are with no known genetic causes. The most commonly associated mutation with acromegaly-causing primary somatotroph adenoma is McCune Albright syndrome – a mutation in the alpha subunit of guanine nucleotide stimulatory protein (G_s protein) gene. Other important familial syndromes associated with acromegaly include MEN-1 (multiple endocrine neoplasia-1), familial isolated pituitary adenoma (defect in tumor suppressor gene AIP) and Carney complex (defect in gene for protein kinase cAMP dependent regulatory subunit alpha) .

EPIDEMIOLOGY

The epidemiology of acromegaly has changed over the past 3 decades. Before the 1990s, the global prevalence rate was reported to be 40 to 60 cases per million persons and the incidence rate was 3 to 5 cases per million person years. More recent reports suggest a prevalence rate of 70 to 90 cases per million persons with incidence increasing and 116.9 new cases added per million persons per year. Acromegaly usually presents at 30 years of age and average age of onset is estimated to be 40 years in males and 45 years in females. Prevalence is higher in North America and Denmark probably due to robust reporting and lower in other regions of the world probably due to underreporting.

CLINICAL PRESENTATION

Most commonly presented clinical features are summarized in **Figure 1**. As per a recent review by Giustina and Colao (2025), approximately 70% of acromegaly patients have identifiable macroadenomas that impinge on the cavernous sinus. Most patients with acromegaly are reported to seek patient care because of physical changes – 21.5% of the surveyed patients sought medical care because of dysmorphic facies (macroglossia, dental diastema or dental gaps, prognathism or enlarged lower jaw), 13.6% visited their physician due to enlarged hands and feet, 7.5% for headache, 28.8% for hypertension, 27.5% due to diabetes, 25.5% for sleep apnea and 15.5% for cardiac hypertrophy. Symptoms that can be missed by physicians resulting in missing an early diagnosis, are discussed in a later section in this manuscript, with a summary in **Table 1**.

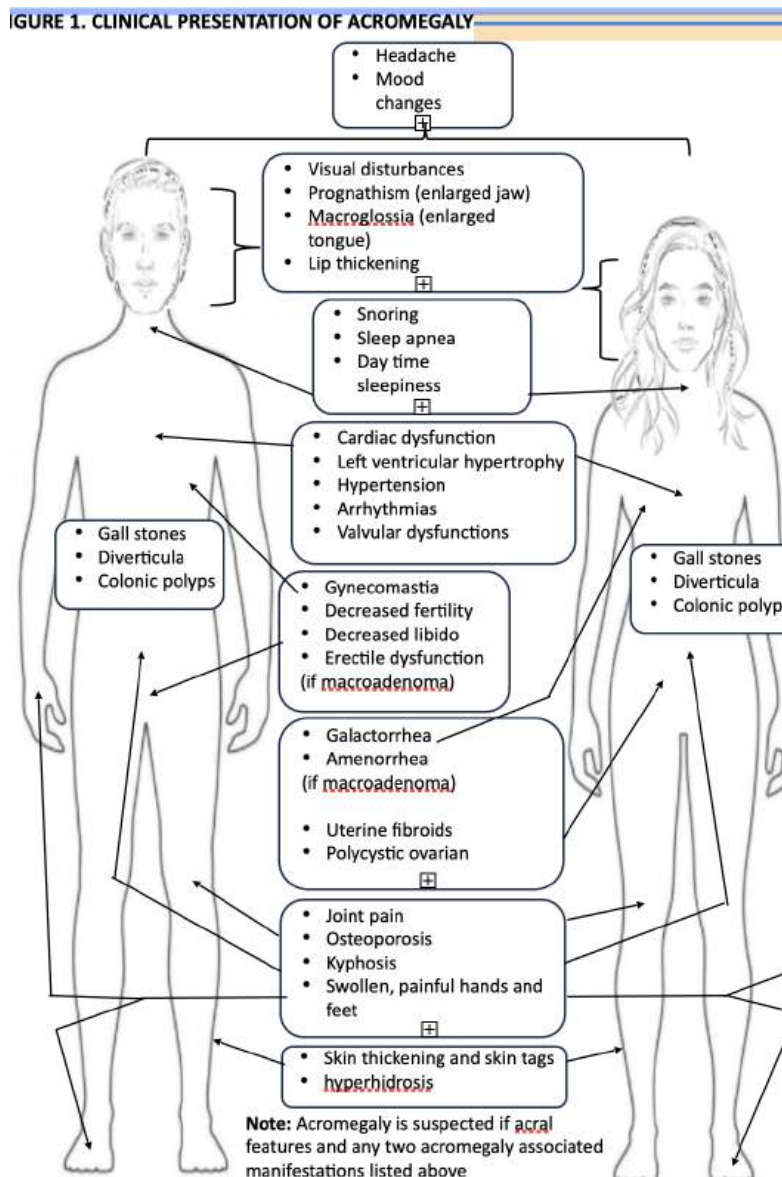


Figure 1. Clinical presentation of acromegaly

PATHOPHYSIOLOGY

Growth hormone secretion by anterior pituitary somatotrophs follows a pulsatile pattern. This secretion is majorly balanced by two hypothalamic hormones – the stimulatory Growth hormone releasing hormone (GHRH) and the inhibitory somatostatin acting through somatostatin receptors SSSTR-2 and SSSTR-5. Regulation is also mediated by several neurotransmitters and a complex interplay of hormonal, neuropeptide and metabolic signals, some of which act directly on the somatotrophs, and others on the hypothalamic growth hormone regulatory hormones. The hormone has a plasma half-life of 20 to 30 minutes and secretion increases with fasting as well as physical exercise while decreases with age and obesity. A circadian rhythm is also reported for the hormone with peak secretion at night, the increase reaching acromegaly levels.

Growth hormone mediates most of its activities through induction of hepatic insulin-like growth factor-1 (IGF-1). IGF-1 has a long plasma-half life and hence is a good marker of growth hormone activity. Both intermediary and bone metabolism effects of growth hormone are mediated by hepatic IGF-1. The pathogenesis of sporadic acromegaly is mediated by oncogenic mechanisms.

Evaluation

Patients with typical phenotypic features and patients with multiple disorders (sleep apnea, hypertension, uncontrolled diabetes mellitus type 2) associated with acromegaly qualify for screening. Screening is not done in patients with isolated disorders like sleep apnea or hypertension alone, for instance. The primary marker for screening is IGF-1 (insulin-like growth factor-1) rather than growth hormone because the latter shows circadian, dietary and sleep-pattern associated variations. A normal IGF-1 rules out acromegaly but an increase in IGF-1 confirms an excess of growth hormone and the next step is to go for imaging to localize the source of hypersecretion. If the IGF-1 results are ambiguous, a growth hormone (GH) suppression test is performed. This is a test involving oral intake of 75 g of glucose by the patient, followed by measurement of growth hormone in the lab before and 2 hours after the intake. If growth hormone concentration is more than 1 ng/ml after the load, acromegaly is confirmed. In addition to IGF-1, GH suppression also yields ambiguous results, other dynamic tests are available but are rarely done and will not be discussed in this paper.

When it comes to imaging, the first choice is pituitary MRI because somatotroph adenoma is the most common cause of acromegaly. A mass in the MRI warrants initiation of treatment. If a mass is not identified, it could mean either presence of a pituitary microadenoma or an extra-pituitary source of GH hypersecretion. In such cases, alternative imaging like CT scan of chest and abdomen or a DOTATE PET scan should be done along with serum measurement of GHRH (growth hormone releasing hormone). An elevated GHRH, usually > 300 ng/ml, suggests an extra-pituitary source of GH hypersecretion.

Since adenomas secrete more than one or multiple hormones and since acromegaly is commonly associated with comorbidities, other tests to be done include serum levels of ACTH, early morning cortisol, free T4, FSH, LH with testosterone or estradiol; hemoglobin A1c for

diabetes mellitus; lipid panel for dyslipidemia; sleep study for sleep apnea; ECG and echocardiogram for symptoms of heart failure; visual field testing for visual disturbances. More about assessment methods to be employed have been discussed in the next section, with a summary in **Table 1**.

ROLE OF CLINICIANS IN THE DIAGNOSIS OF ACROMEGALY

Diagnosis is more often than not missed by primary care physicians because of the insidious onset of the disease- slowly evolving changes are easily missed because the same physician sees the patient over time. Primary care physicians and their healthcare team members encompassing nurse practitioners, physician assistants can play an important role in the early diagnosis of acromegaly in patients with acral enlargement, especially those with minimum two signs/symptoms associated with acromegaly (as illustrated in **Figure 1**). When primary care physicians suspect acromegaly, a biochemical lab investigation as explained above in the section “Evaluation” needs to be done. Specialists may also miss early diagnosis because of the slow progressive nature of the disease and their role in diagnosis of acromegaly is discussed in detail below.

Gynecologists may be among the first specialists to see premenopausal females with acromegaly since they visit the office for menstrual disturbances – acromegaly is commonly associated with uterine leiomyomas (usually multiple), ovarian cysts, infertility as well as hypogonadism and/or hyperprolactinemia (due to mass effect of the tumor). It needs to be remembered here that hypopituitarism could be subtle in these patients. A pelvic ultrasonography would help in diagnosis.

Endocrinologists may prove useful in picking glucose intolerance or diabetes at diagnosis. Glucose tolerance test and dual x-ray absorptiometry (to detect acromegaly-related lipodystrophy with reduced visceral adipose tissue and ectopic lipid deposition in muscle) may prove useful diagnostic methods.

Cardiologists could play an important role in diagnosis because acromegaly patients commonly present with hypertension, valvular dysfunctions and arrhythmias. Acromegalic cardiomyopathy characteristically presents as concentric left ventricular hypertrophy associated initially with diastolic and later with systolic dysfunction. Hypertension is the most common cause of death due to cardiovascular causes in patients with acromegaly. Echocardiography, electrocardiography and/or 24-hour electrocardiography, 24-hour blood pressure measurement are the assessments that need to be employed by cardiologists.

Rheumatologists and orthopedists have early acromegaly patients often referred to them by primary care physicians since 70% of the patients present with progressive functional disability and compromised quality of life caused by large joint pain and axial arthropathy. MRI findings in acromegaly patients with arthropathy include very thick joint cartilage with increased water content. Tiny cysts and bone marrow lesions are also seen. When patients with normal or mildly reduced bone mineral density present with vertebral fractures, or when patients present with bilateral or recurring carpal tunnel syndrome, it warrants referral to an orthopedist. DXA,

vertebral radiography, MRI of joints and upper limb electromyography are the useful assessment tools.

Colonic polyps, advanced adenomas and colorectal carcinomas are common in acromegaly patients and hence oncologists may be the first to recognize acromegaly in a patient.

A cardinal feature of acromegaly, which is headache, is due to the mass effect of the tumor on duramater and pain producing structures. Headaches are caused by GH-secreting microadenomas as well. However, the latter headaches respond well to somatostatin receptor analogs. Cluster headaches and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing are reported in acromegaly patients. These headaches show limited response to conventional treatment and may even lead to depression in these patients. A brain MRI may need to be employed.

A summary of symptoms that can be missed by the respective specialists and assessment methods that need to be employed are summarized in **Table 1** below.

Table 1. What clinicians can miss in acromegaly and useful assessment methods (Adopted from NEJM article by Giustina and Colao, 2025)		
Specialist	Signs/ symptoms that are missed	Useful assessment methods
Gynecologist	Multiple uterine leiomyomas, polycystic ovarian morphology	Pelvic ultrasonography
Endocrinologist	Insulin resistance and lipodystrophy	Glucose tolerance test, DXA
Cardiologist	Left ventricular hypertrophy, valvular dysfunctions, QT-wave prolongation	Echocardiography, ECG and/or 24-hour ECG, 24-hour blood pressure measurement
Rheumatologist/ Orthopedist	Large-joint pain, vertebral fractures, relapsing carpal tunnel syndrome	DXA, vertebral radiography, MRI of joints and upper limb electromyography
Oncologist/ gastroenterologist	Colonic polyps, adenomas and cancers	Colonoscopy, abdominal ultrasonography
Neurologist/ psychiatrist	Headache, Depression	Brain MRI
Pulmonologist	Snoring, sleep apnea, breathing impairment	Polysomnography, spirometry
Dentist, otolaryngologist	Macroglossia, prognathism, dental diastema	Panoramic radiography of the mouth, cone beam CT
Ophthalmologist	Visual disturbances	Visual field testing

TREATMENT

Surgical, medical and radiation therapies are the main line of treatment in acromegaly. Treatment goal is removal or control of the adenoma, normalizing IGF-1 and growth hormone levels, preservation of anterior pituitary function and normalization of life expectancy.

Pituitary surgery is the treatment of choice for most people with acromegaly if an expert surgeon is available. Biochemical control has been seen post-surgery in 75% of patients with microadenomas and 50% of patients with macroadenomas. These outcomes are expected to further improve in future with the use of advanced imaging, augmented reality imaging and AI techniques. Surgery is not recommended if there is cavernous sinus invasion unless crucial regions in the surrounding are endangered, because there are low chances of complete removal of the adenoma. Surgery will need to be delayed in patients with upper airway obstruction, severe hypertension, poorly controlled diabetes mellitus or heart failure. These need to be managed properly before scheduling any surgery.

The first line of medical treatment is with somatostatin receptor analogs that preferentially act on somatostatin receptor 2 (SSTR-2). Most commonly used SSTR-2 analogs are octreotide long-acting repeatable and lanreotide auto gel, the former used as intramuscular monthly injections and the latter as deep, subcutaneous injections. Because of their efficacy they are the first line of treatment where surgery fails or the full effect of radiation therapy is pending. In patients that do not respond fully, increasing the dose or frequency is effective in achieving hormonal normalization. Poor acceptability and lack of adherence are the major concerns associated with octreotide injectable and lanreotide. CAM2029 is a self-injectable form of subcutaneous octreotide depot and does not need the role of healthcare professionals in its administration. FDA approved oral octreotide capsules are available for use in patients who showed acceptable side effect-profile to octreotide long-acting injectables. Pasireotide long-acting release, a SSTR-2 as well as SSTR-5 analog, when injected intramuscular monthly, is more effective in normalizing the hormonal profile. However, it needs to be given with GLP-1 (glucagon-like polypeptide) receptor agonists because it increases insulin and incretin secretions and can frequently cause hyperglycemia and diabetes. Pasireotide is the second line of treatment in acromegaly patients without diabetes or those who have residual adenoma remnants after surgery. It is the first line of choice in patients that express only or primarily SSTR-5.

Among other medical treatments in acromegaly are pegvisomant, a pegylated growth hormone analog; cabergoline, a dopamine agonist, for prolactinoma; and combination treatments like pegvisomant-SSR agonist to reduce the injection burden or pegvisomant-SSR agonist or cabergoline-pegvisomant to improve efficacy of treatment.

Radiotherapy is the third line of treatment after failure of surgical and medical treatment. Conventional radiotherapy administered over several weeks is used for larger tumor masses but is associated with increased risk of cerebrovascular and pituitary damage. Stereotactic radiosurgery is a gamma knife-enabled single administration and is used for smaller masses that do not invade the optic chiasm.

SOCIAL IMPLICATIONS AND QUALITY OF LIFE

Diagnostic delay and therapeutic inertia (failure to change treatment if initial treatment fails to meet the treatment goal) are two risk factors that directly affect the natural history and outcome of acromegaly. These are modifiable risk factors so timely diagnosis and modification to treatment, if achieved, can quickly achieve hormonal control, minimize the time during which IGF-1 remains elevated, reverse most of the manifestations of acromegaly and bring down the risk of death.

Despite effective treatment, most comorbidities persist or even progress. For instance, hypertension, left ventricular hypertrophy and sleep apnea may be decreased but do not disappear after successful normalization of IGF-1. Similarly, vertebral fractures do occur in patients with normalized IGF-1. On the contrary, hyperglycemia, soft tissue hypertrophy and carpal tunnel syndrome get managed to resolution when acromegaly is controlled. Owing to these variations in response to therapy, poor quality of life persists in acromegaly patients, particularly those on medical treatment. Treatments aimed at resolving comorbidities that are currently not resolving with IGF-1 normalization, is the need of the hour.

Survival rates among acromegaly factors are dictated by geographic factors, health care system, length to diagnosis, length of follow-up, healthcare system. Lower mortality rates are reported in recent years and may be owed to improved treatment, implementation of global guidelines, improved follow-up of comorbidities and use of modern disease-staging tools. In contrast, increased standardized mortality rates due to cardiovascular and oncological causes are still reported in subpopulations with diagnostic delay of more than 10 years.

CONCLUSION

Acromegaly is a rare, progressive disease with an insidious onset. This very nature of the disease makes diagnostic delay a common factor in determining its local and systemic manifestations. Major adverse effects on quality of life and survival still persists. IGF-1 is the gold standard for screening of acromegaly. Diagnostic delays are likely to be minimized in the coming times owing to improved scoring and AI systems for screening and recognizing acromegaly facies, and more adequate information for the treater and the treated. Although multimodal treatment regimens are available, the disease is hard to control in some patients given the tumor features, poor adherence to treatment, ineffective treatment, adverse effects or combinations of these factors. This poses a challenge to improve the quality of life and reduce mortality in acromegaly patients. Modern surgical techniques, increased access to molecular profiling of tumors, newer and more efficient treatment with better adherence and improved clinical monitoring during follow-up may help achieve better outcomes in the coming times.

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