REVIEW ARTICLE

Acromegaly

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CME

Pituitary tumors account for approximately 15% of intracranial neoplasms and may (in the case of macroadenomas, which have a diameter >10 mm) cause compression of surrounding structures, as well as systemic symptoms. Acromegaly is the result of excess growth hormone secretion by generally benign adenomas arising in adult pituitary somatotrophs. Extrapituitary causes are exceedingly rare. The incidence of acromegaly is approximately 10 cases per 1 million persons.[1] Roughly 20% of all pituitary tumors secrete growth hormone (somatotroph adenomas), and 95% appear to be sporadic, without known genetic causes. Approximately 25% of somatotroph adenomas also secrete prolactin.[2] In this article, we review current knowledge of the pathophysiology and pathogenesis of acromegaly, as well as its clinical features, diagnosis, treatment, and disease course, focusing on the general clinician's key role in early diagnosis and management.

PHYSIOLOGY AND PATHOGENESIS

Growth hormone is secreted in a pulsatile fashion by the pituitary gland and is orchestrated by two hypothalamic peptides: growth hormone–releasing hormone, which stimulates secretion, and somatostatin, which inhibits secretion through specific receptors (i.e., subtypes classified as somatostatin receptor [SSTR]-2 and SSTR-5). Several neurotransmitters — but also hormonal, metabolic, and neuropeptide signals, acting directly on somatotrophs or indirectly through hypothalamic hormones — modulate growth hormone secretion (half-life, 20 to 30 minutes), which increases with fasting and physical exercise and decreases with age and obesity.[3]

Normally, growth hormone circulates in low concentrations but peaks intermittently, mainly at night, reaching levels that overlap with those found in acromegaly. Growth hormone induces hepatic secretion of insulin-like growth factor I (IGF-I), which mediates most growth hormone actions. Since IGF-I has a long half-life, it is a good marker of growth hormone secretory activity. The growth hormone–IGF-I axis in adults participates in regulation of both intermediary and bone metabolism.[4] Several oncogenic mechanisms that have been identified by genomic, epigenomic, and transcriptomic studies are thought to contribute to the pathogenesis of sporadic acromegaly.[5]

CLINICAL PRESENTATION AND DIAGNOSIS

At diagnosis, approximately 70% of patients with acromegaly have identifiable macroadenomas that may have grown laterally and extend into the cavernous sinus.[6] In the large Liège Acromegaly Survey,[7] physical changes were most often what led patients with acromegaly to seek medical evaluation and care, especially the development of dysmorphic facies (in 21.5% of cases), which were associated with macro-

KEY POINTS

ACROMEGALY

- Acromegaly is a chronic, disfiguring disease that leads to a poor quality of life and decreased survival as a result of multiple coexisting systemic conditions.
- Diagnostic delay — even a delay of 10 years or more — is common and is a major determinant of disease severity.
- The role of clinicians in reducing diagnostic delay is crucial, since specific findings occur in multiple organs and should trigger a suspicion of acromegaly early in the disease course.
- Once acromegaly is suspected, the clinician evaluating the patient should order an insulin-like growth factor I assay.
- Multimodal treatment is often needed to control acromegaly, and new medical agents may improve both therapeutic efficacy and treatment adherence.

glossia, dental diastema (gaps), mandibular overgrowth, and prognathism[8] (Fig. 1), and enlarged hands and feet (in 13.6%). Headache (in 7.5% of cases), asthenia (in 5.9%), and excess perspiration (in 2.0%) also led patients to seek care.[7] Coexisting conditions noted at diagnosis included thyroid enlargement (in 34.0% of cases), hypertension (in 28.8%), diabetes (in 27.5%), sleep apnea (in 25.5%), and cardiac hypertrophy (in 15.5%) (Fig. 2).[7]

EFFECTS OF DIAGNOSTIC DELAY

A substantial delay between the development of initial symptoms and diagnosis is a common problem that has decreased only slightly over several decades. Diagnostic delays currently exceed 5 years, on average, with a delay of more than 10 years in 25% of cases.[9] Coexisting conditions (an average of roughly four per patient), as well as increased mortality, are directly correlated with a delayed diagnosis and are more common in older patients, particularly women. In fact, the signs and symptoms of acromegaly, often characterized by a slow, insidious onset, may be inappropriately attributed to aging or menopause.[9] In a survey of patients with acromegaly, almost 60% of the respondents reported that the disorder had been misdiagnosed, and almost a quarter reported a diagnostic delay, which patients believed was due, in part, to limited awareness among nonspecialists.[10] A delayed diagnosis was associated with high growth hormone levels at diagnosis, as well as coexisting musculoskeletal and cardiovascular disorders. The earliest systemic manifestations before diagnosis are hypertension (mean [±SD] interval between onset and diagnosis, 6.6±7.5 years) and carpal tunnel syndrome (5.7±6.7 years).[11] Vertebral fractures, detected in 30% of patients at presentation,[12] are strongly associated with a diagnostic delay.[13]

Clinical screening tools are available that could facilitate earlier diagnosis of acromegaly, such as ACROSCORE, a 14-point scoring system that accounts for diabetes and carpal tunnel syndrome, among other features.[14] However, one must have a clinical suspicion of acromegaly to think of using this instrument. Newer analytic techniques that are applied to claims databases, such as data mining and machine learning, might also become tools to support an early diagnosis of acromegaly.[15,16] Collaboration with patient advocacy groups may help to spread key information about acromegaly and its dangers to the general population and promote earlier referral for diagnostic testing.[17] IGF-I assessment in primary care practice[18] is currently cost-ineffective,[19] and published studies of artificial intelligence (AI)–based methods have been relatively small and lack sufficient racial and ethnic diversity, which arouses concerns about the accuracy and the clinical usability of AI-based algorithms involving facial image analysis.[20] Consensus guidelines recommend IGF-I measurement in patients with a pituitary mass or signs of possible acromegaly, such as increased sweating or a change in ring or shoe size.[19]

IMPORTANT ISSUES FOR THE NONSPECIALIST

A patient-reported outcome study indicated that on average, more than three physicians were consulted before acromegaly was diagnosed,[21] which strongly suggests insufficient knowledge of the disease among nonendocrinologists. Thus, further education is needed.[22]

Primary care physicians or other persons working in primary care settings (e.g., nurse practitioners and physician assistants) can play key roles in considering the possibility of acromegaly in patients with acral enlargement, particularly those with at least two signs or symptoms associated with acromegaly. Primary care clinicians often do not consider acromegaly, which evolves slowly. Since patients are usually seen by the same general practitioner over time, slowly evolving changes

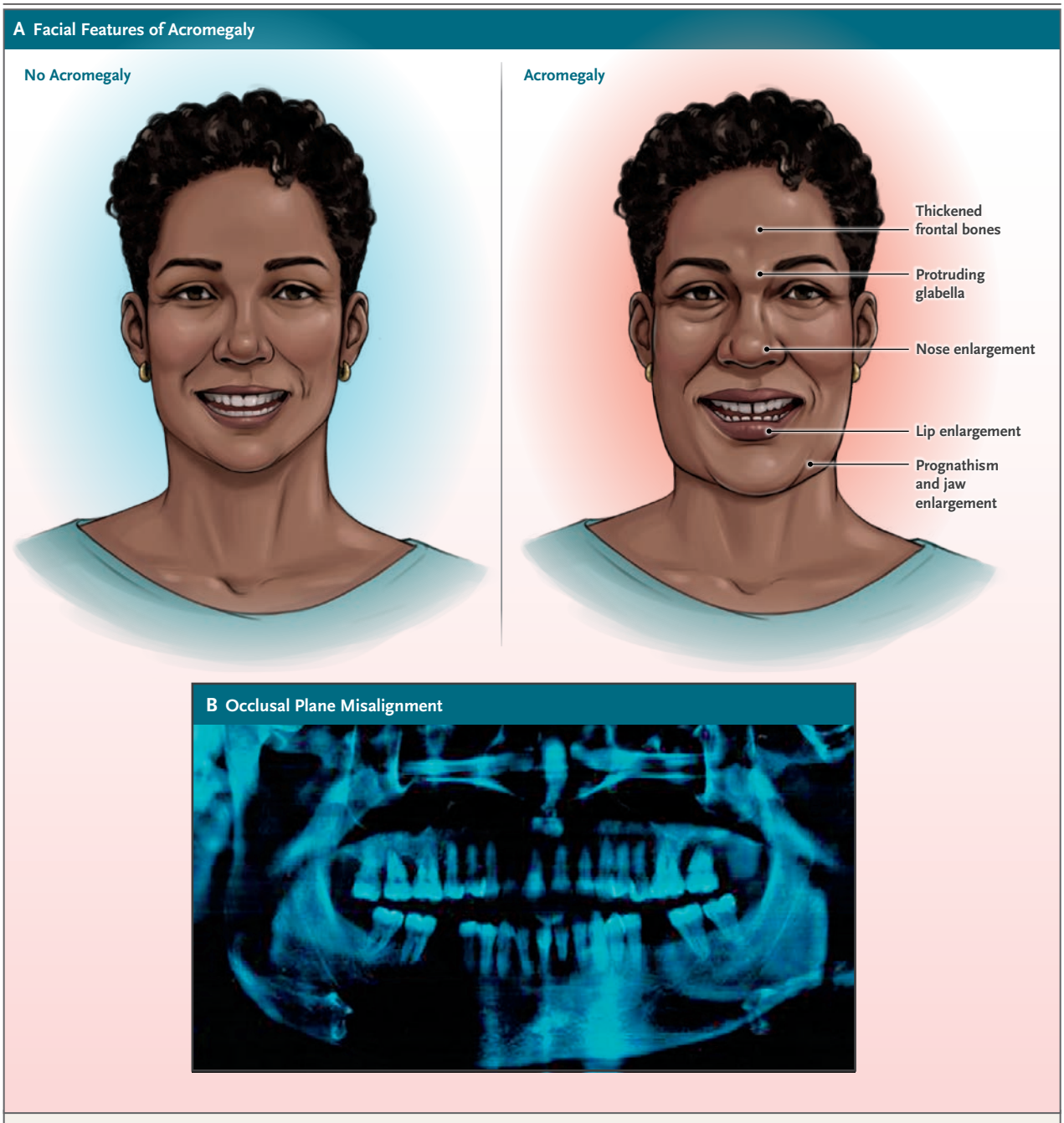


Figure 1. Facial Features of Acromegaly.

Panel A is an artist's rendering of the facial features of acromegaly. Panel B shows radiographic orofacial findings in a representative patient with acromegaly.

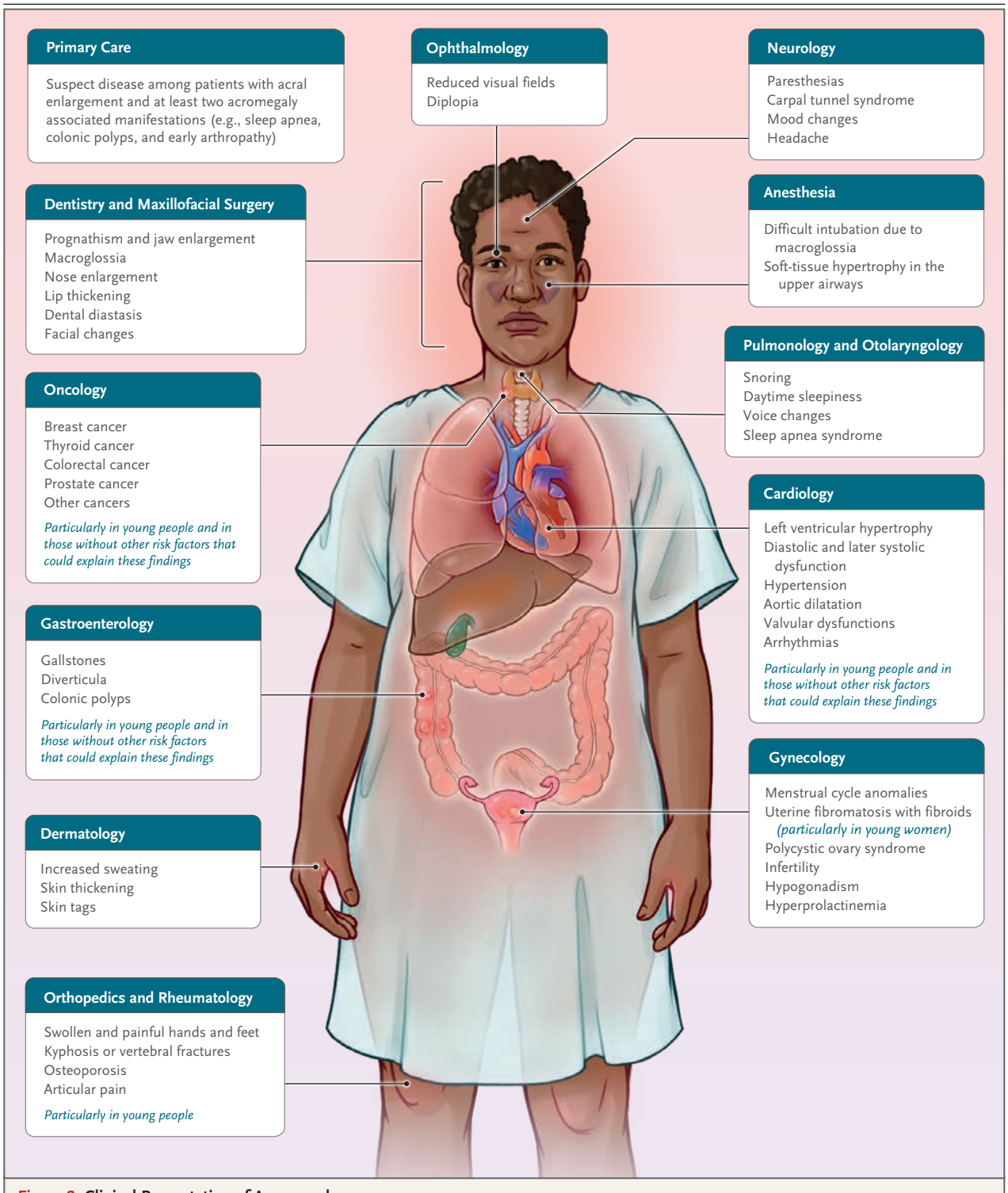


Figure 2. Clinical Presentation of Acromegaly.

Specialists outside of endocrinology may be involved in the diagnosis of acromegaly. Specific manifestations occur in multiple organs and should trigger a suspicion of acromegaly early in the disease course. Men with acromegaly may be seen by a urologist for prostate hypertrophy or erectile dysfunction.

are easily missed.[23] Indeed, specialists may also miss the diagnosis (Table 1).

Gynecologists may be among the first clinicians to see premenopausal women with acromegaly, most commonly for menstrual disturbances. Uterine leiomyomas (particularly if more than one is present), ovarian cysts, and infertility may be found in association with acromegaly.[24] Hypopituitarism may be subtle, and hypogonadism occurs in approximately half of patients with acromegaly as a result of the mass effect of the tumor, hyperprolactinemia, or both.[22]

Structural and functional cardiac abnormalities may develop in patients with acromegaly.[25] Acromegalic cardiomyopathy (Fig. 3) is characterized by concentric left ventricular hypertrophy associated with diastolic and, in later stages, systolic dysfunction.[26] At the time of diagnosis, it is not unusual for a patient to have hypertension, valvular dysfunctions (mainly aortic, mitral, and tricuspid insufficiency), and arrhythmias.[27-29] The major contributor to death from cardiovascular causes in patients with acromegaly is hypertension,[30] which has a prevalence ranging from 30 to 60% among such patients.[31] Echocardiographic and electrocardiographic signs[28,32,33] that should alert cardiologists are noted in Table 1.

Rheumatologists or orthopedists see patients with early acromegaly who have been referred by primary care doctors because of large-joint pain and axial arthropathy, since up to 70% of patients have such symptoms along with progressive functional disability, often with a compromised quality of life by the time of the referral.[34] Distinctive findings on magnetic resonance imaging (MRI) in patients with acromegaly-associated arthropathy include excessively thick joint cartilage with increased water content and small cysts and bone marrow lesions.[35] Orthopedic surgeons may be consulted about patients who have vertebral fractures with normal or slightly reduced bone mineral density (Fig. 4)[22] or patients with bilateral or relapsing carpal tunnel syndrome[36] (Table 1).

An oncologist may be the first to realize that a patient has acromegaly, given the increased risk of various types of cancer among patients with acromegaly.[37] In particular, retrospective colonoscopy studies have shown that colonic polyps,

Table 1. Signs and Symptoms of Acromegaly That Are Often Missed.*

Signs and Symptoms	Clinician Involved	Assessment
Recent-onset dysglycemia, insulin resistance, lipodystrophy	Endocrinologist†	Oral glucose tolerance test, DXA‡
Malocclusion, dental diastema, macroglossia, prognathism	Dentist, orofacial surgeon, otolaryngologist	Panoramic radiography of the mouth, cone beam CT
Snoring, daytime sleepiness, sleep apnea syndrome, breathing impairment	Pulmonologist, technician performing testing	Polysomnography, spirometry
Large-joint pain; enlarged hands and feet; kyphosis, vertebral fractures, or osteoporosis; bilateral or relapsing carpal tunnel syndrome	Orthopedist, rheumatologist, physical therapist	DXA, vertebral radiography, joint MRI, upper-limb electromyography
Multiple uterine leiomyomas, polycystic ovarian morphology	Gynecologist	Pelvic ultrasonography
Colonic polyps or cancer, other type of cancer	Gastroenterologist, oncologist	Colonoscopy; mammography; thyroid, prostate, or abdominal ultrasonography
Impaired vision	Ophthalmologist	Visual-field testing
Left ventricular hypertrophy (even with mild hypertension); aortic, mitral, or tricuspid insufficiency; QT-interval prolongation	Cardiologist	Echocardiography; ECG, 24-hr ECG recording, or both; 24-hr blood pressure measurement
Headache, depression	Neurologist, psychiatrist	Brain MRI

* CT denotes computed tomography, ECG electrocardiography, and MRI magnetic resonance imaging.
† Endocrinologists also may miss these signs and symptoms but do so less often than other clinicians. However, endocrinologists may see some of these patients first, given the onset of dysglycemia, as noted.
‡ An oral glucose tolerance test is also used for the diagnosis of acromegaly (except in patients with known diabetes). Dual-energy x-ray absorptiometry (DXA) is also used for the diagnosis of osteoporosis.

particularly multiple polyps or polyps in the left colon, as well as advanced adenomas and colorectal carcinomas, are more common in patients with acromegaly than in patients without acromegaly[37-39] (Table 1 and Fig. 5).

The highly prevalent symptom of headache in patients with acromegaly appears to be due to stretching of the dura mater and invasion of pain-producing structures, but patients with growth hormone–secreting microadenomas may also present with severe headache that responds well to somatostatin receptor ligands.[40] Patients may present with unusual headache phenotypes, such as cluster headaches and unilateral short-lasting neuralgiform headache attacks with conjunctival injection and tearing[41] and a limited response to conventional treatment, as well as with depression.[42]

Thirty to 50% of patients with acromegaly have glucose intolerance or diabetes at diagnosis.[43] Dual x-ray absorptiometry can detect specific acromegaly-related lipodystrophy with reduced visceral adipose tissue and ectopic lipid deposition in muscle[44] (Table 1).

Sleep apnea and disordered breathing have been detected with polysomnography in up to 80% of patients with newly diagnosed acromegaly, even those with normal weight or mild overweight. These disorders are mainly due to obstruction caused by acromegaly-associated craniofacial anomalies, macroglossia, and laryngeal-wall thickening,[45] which may also lead to heavy snoring.[46] Acromegaly has also been diagnosed after difficult intubation[47] (Table 1). Dermatologists may be the first to see patients with acromegaly who have typical skin manifestations (multiple skin tags, acne, oily and thickened skin, and acanthosis).[48]

BIOCHEMICAL ABNORMALITIES LEADING TO THE DIAGNOSIS

Primary care clinicians who suspect acromegaly should obtain an initial biochemical evaluation but often request only a growth hormone assay. Random measurements of growth hormone levels, however, are diagnostically unreliable because of the pulsatile nature of growth hormone secretion.[3] Furthermore, many laboratories provide inappropriately wide "normal" ranges, which are based on statistical considerations rather than on pathophysiological health implications.[49] It would be useful if laboratory reports routinely noted that random growth hormone levels are of poor diagnostic value for acromegaly and emphasized the need for additional testing (e.g., IGF-I and post–glucose load growth hormone levels). Since assays for growth hormone may produce misleading results with respect to acromegaly, nonendocrinologists may assume that a suspicion of acromegaly was unfounded. Given such a possibility, age-adjusted IGF-I levels would be the best standard for the diagnosis of acromegaly.[19] The simplest approach is to measure IGF-I when there is a clinical suspicion of acromegaly. Possible caveats in interpreting the results of IGF-I and growth hormone tests include assay inaccuracies and spurious results in patients taking combined oral contraceptives and those with uncontrolled diabetes, severe liver disease, or malnutrition.[49] Measurement of growth hormone levels after a glucose load, global pituitary function tests, and pituitary MRI imaging with gadolinium should then be carried out to complete the diagnostic process.[17]

TREATMENT

TREATMENT GOALS

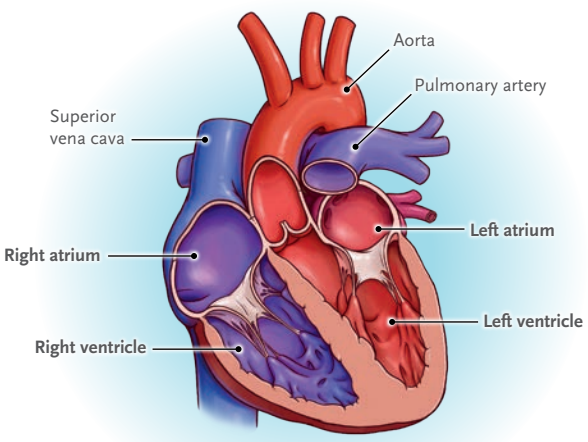
The goals of treatment for patients with acromegaly include removal or control of a pituitary adenoma, normalization of both IGF-I levels (for the patient's age) and growth hormone levels (random levels, <1 μg per liter, or 0.4 μg per liter during an oral glucose tolerance test), prevention of associated conditions, preservation of anterior pituitary function, and normalization of life expectancy through surgery, medical treatment, and radiation therapy.[50]

SURGERY

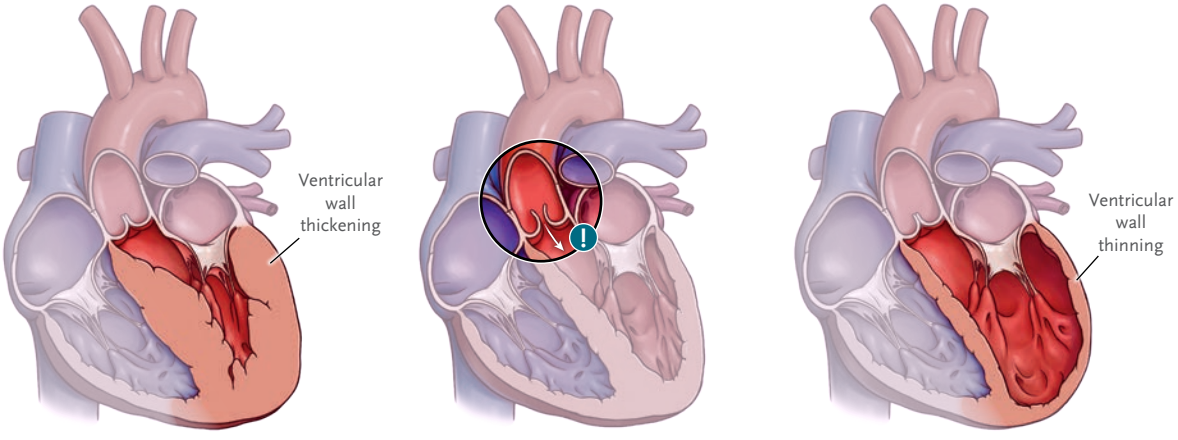
Pituitary surgery is the first-line treatment option for most people with acromegaly, provided that an expert surgeon capable of performing either microsurgical or endoscopic approaches is available.[50] At experienced centers, surgery results in biochemical control in more than 75% of patients with microadenomas and in approximately half of those with macroadenomas.[51] The use of advanced imaging and augmented reality techniques, as well as AI, may improve surgical outcomes in the near future.[52] In patients with cavernous sinus invasion, surgery is not recommended as first-line therapy unless vital structures are endangered, since there is a low likelihood of complete

A Main Cardiac Features of Acromegaly

Normal Heart



Acromegalic Cardiomyopathy



Left Ventricular Hypertrophy | Valvular Dysfunction | Dilated Cardiomyopathy

B Cardiac Ultrasound Findings in a Representative Patient

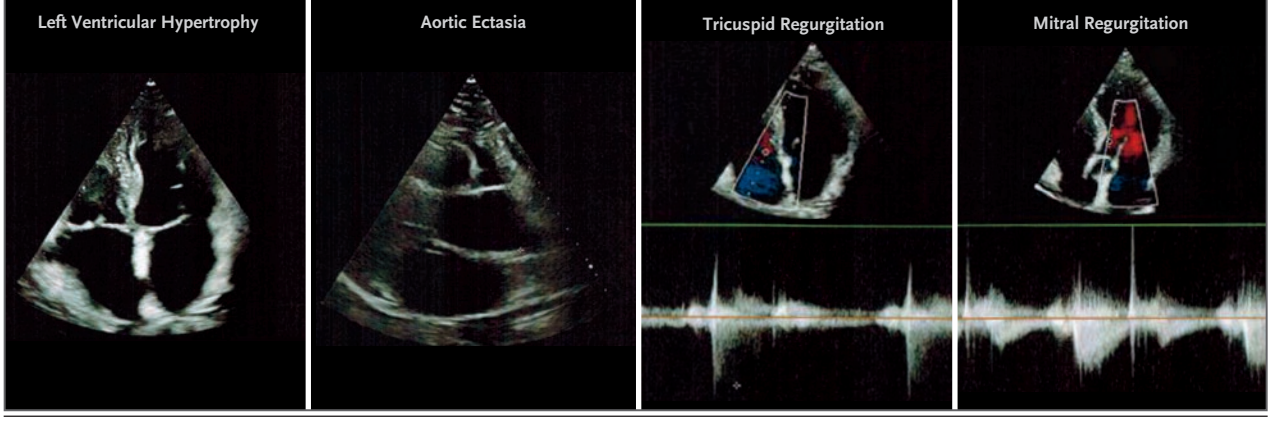


Figure 3 (facing page). Main Cardiac Features of Acromegaly.

Panel A shows the main cardiac features of acromegaly. The exclamation point (middle image) indicates aortic insufficiency. Panel B shows cardiac ultrasound findings in a representative patient with acromegaly.

adenoma removal.[50] Upper-airway obstruction, poorly controlled diabetes, severe hypertension, or heart failure, if present, should be appropriately managed medically, which may require a delay in surgery.[50]

Presurgical treatment with somatostatin receptor ligands may ameliorate some symptoms and induce tumor shrinkage,[53] although this approach is not currently the standard of care.[50] In an audit of international centers, the readmission rate after pituitary surgery was, on average, slightly higher than 2%, though postoperative deficiencies of vasopressin, gonadotropins, and thyrotropin were sporadically observed.[51] Surgical removal of at least 75% of a growth hormone–secreting macroadenoma may enhance the efficacy of subsequent treatment with somatostatin receptor ligands.[54]

MEDICAL TREATMENT

Parenteral Somatostatin Receptor Ligands

Octreotide long-acting repeatable and lanreotide autogel are the available long-acting somatostatin receptor ligands that bind preferentially to SSTR-2. Monthly intramuscular injections of octreotide or deep, subcutaneous injections of lanreotide maintain biochemical control in 30 to 50% of patients, and higher estimates for efficacy are generally reported in studies involving patients who were preselected for their positive response to short-acting octreotide, as compared with unselected patients.[55]

As a result of their efficacy-to-safety ratio, these drugs are widely used as first-line medical

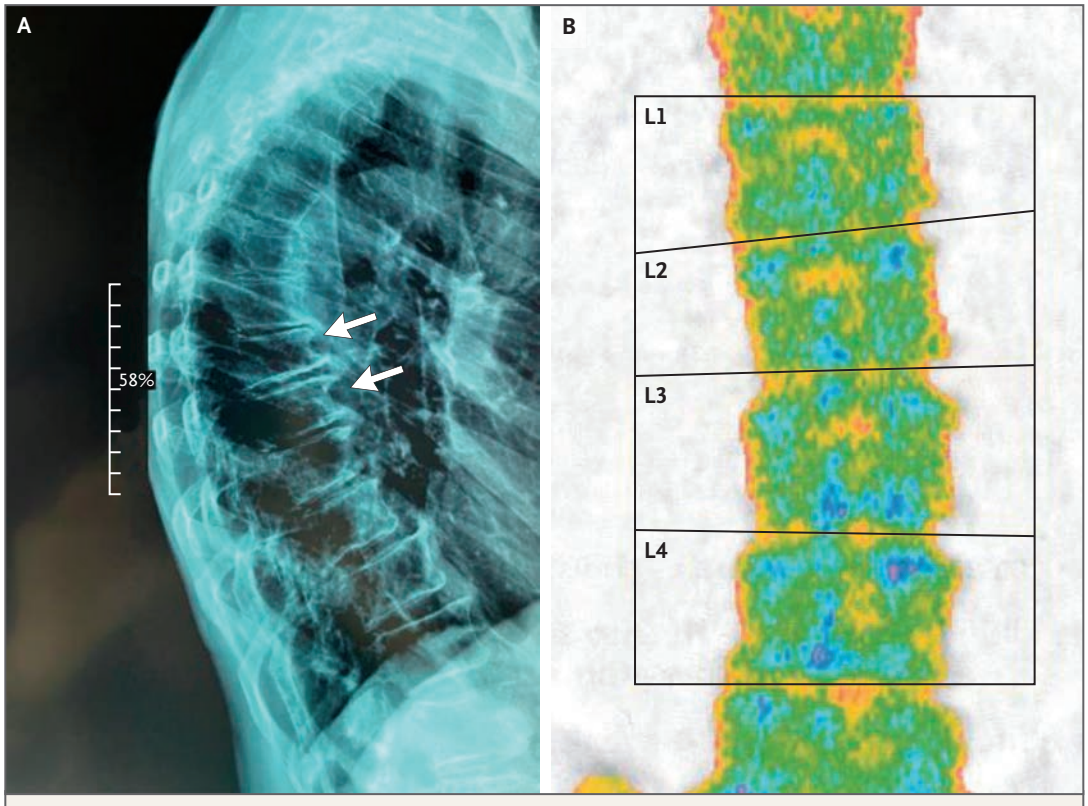
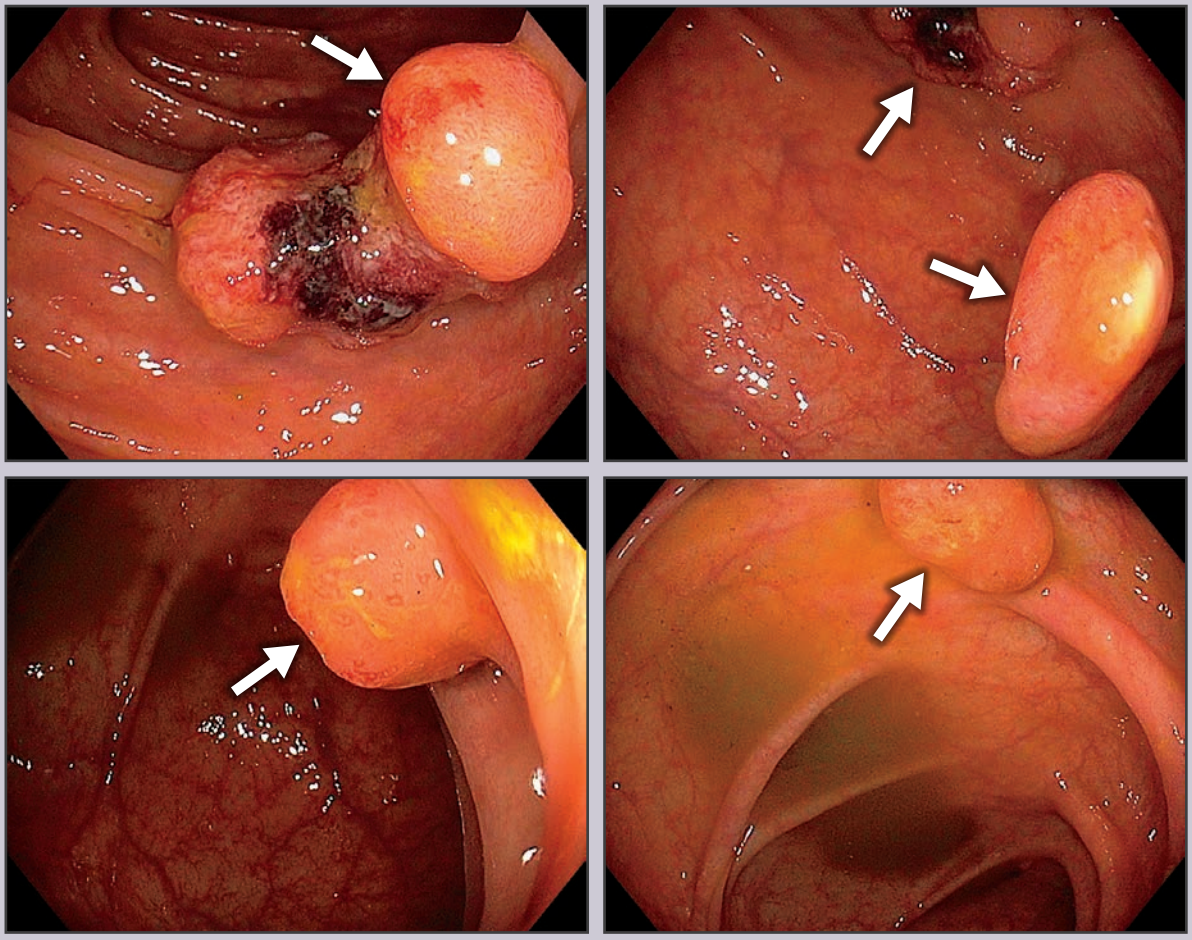


Figure 4. Vertebral Fractures in a 52-Year-Old Man with Controlled Acromegaly.

The patient, in whom acromegaly was controlled with medical therapy, had vertebral fractures (T8 wedge, moderate, 30%; T9 wedge, mild, 22%) on second-line morphometric assessment on lateral thoracic spine radiography (Panel A), with apparently normal bone mineral density (mean T score, −0.9 SD) at the lumbar spine on a dual-energy x-ray absorptiometry (DXA) scan (Panel B).

A Colonoscopy in a Representative Patient Showing Multiple Colon Polyps



B Infiltrating Colon Adenocarcinoma

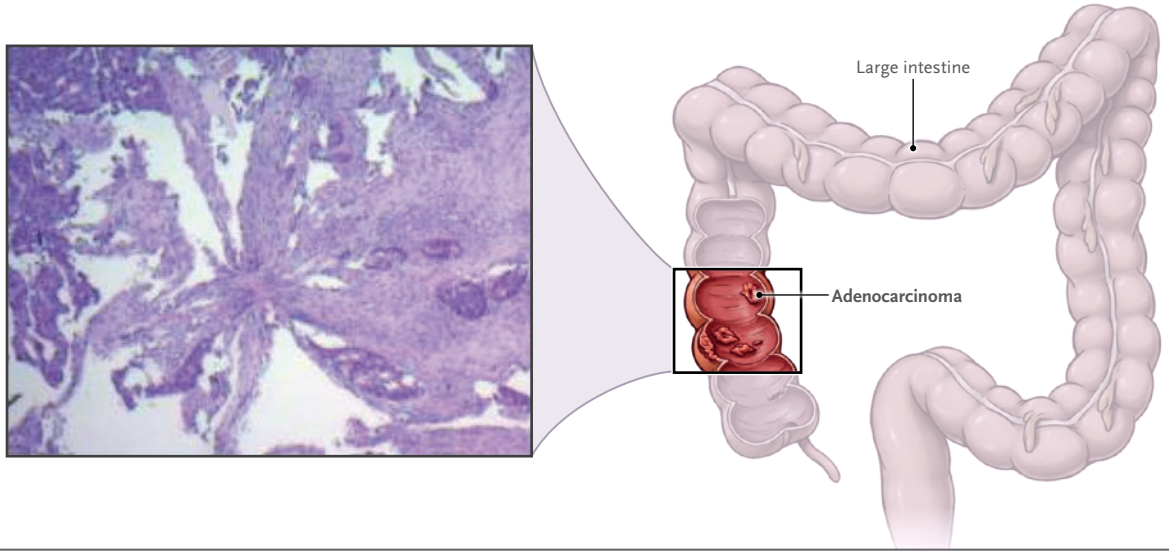


Figure 5 (facing page). Colonic Polyps in a Patient with Uncontrolled Acromegaly.

A colonoscopy performed in a 63-year-old man with uncontrolled acromegaly showed multiple polyps (Panel A). A histologic section of one of the biopsied lesions revealed an infiltrating adenocarcinoma of the ascending colon (Panel B, hematoxylin and eosin staining). Histologic image of colonic adenocarcinoma courtesy of Antonio Vetrani.

treatment after surgical failure or pending the full effect of radiation therapy.[50] Somatostatin receptor ligands may induce tumor shrinkage by 20% or more in around 50% of patients,[56] as well as safely improving the clinical picture,[51] since abdominal discomfort and steatorrhea are often, although not always, transient.[57] Abnormalities of glucose metabolism have little importance in most patients, and gallstones seen on liver ultrasonography (which is generally routinely performed in patients with acromegaly) are usually asymptomatic.[51] In 30% of patients who do not have a complete response to standard maximal doses of octreotide long-acting repeatable or lanreotide autogel, increasing the dose or frequency of injections may safely normalize IGF-I levels.[58]

Currently, the major issues with octreotide and lanreotide include poor acceptability and lack of adherence (because of the need for long-term use) among patients whose disease is controlled and lack of disease control among others. Pasireotide long-acting release, a somatostatin receptor ligand that binds both SSTR-2 and SSTR-5 and is given as monthly intramuscular injections, has been reported to be more effective in normalizing the hormonal profile than octreotide long-acting repeatable,[59] with improved biochemical responses in patients for whom previous treatment with other somatostatin receptor ligands did not provide hormonal control.[60] Such an approach has efficiently induced adenoma shrinkage.[61] However, unlike octreotide and lanreotide, pasireotide can frequently cause hyperglycemia or diabetes because of decreases in both insulin and incretin secretion, a problem that occurs in more than half of patients, particularly in those with preexisting hyperglycemia. Glucagon-like peptide 1 (GLP-1) receptor agonists can control pasireotide-mediated hyperglycemia.[62] Pasireotide is currently indicated as a second-line medical treatment in patients without diabetes who have relevant residual adenoma remnants after surgery.[63] With wider use of molecular profiling of pituitary tissue, however, this drug might be a first choice for patients with adenomas that express only SSTR-5 or mostly SSTR-5.

Octreotide long-acting repeatable and, to a lesser extent, lanreotide autogel generally need to be administered by health care personnel. However, CAM2029, a novel investigational form of subcutaneous octreotide depot, which was developed on the basis of fluid crystal technology, enables self-injection. In a 6-month phase 3, double-blind, randomized, placebo-controlled trial involving patients who had had a response to once-monthly somatostatin receptor ligand injections, the percentage of patients in whom IGF-I levels were controlled was higher with CAM2029 than with placebo.[64]

Oral Drugs

The development of transient permeation enhancer technology has made it possible to formulate oral octreotide as capsules. This technology facilitates oral absorption by transiently opening tight junctions between enterocytes, which protects the drug from degradation in the gastrointestinal tract. Oral octreotide capsules were approved by the Food and Drug Administration for long-term treatment of acromegaly in patients whose disease was controlled by octreotide long-acting repeatable or lanreotide autogel with an acceptable side-effect profile, on the basis of clinical trials in which the capsules maintained biochemical control in approximately two thirds of the patients and improved clinical status after a switch from injectable somatostatin receptor ligands, with a similar safety profile.[65] A recent phase 3, double-blind, randomized, placebo-controlled trial compared paltusotine, an oral, selective, nonpeptidic SSTR-2 ligand, with placebo in patients with acromegaly that was controlled with stable depot octreotide or lanreotide treatment.[66] After a randomized switch from somatostatin receptor ligands to paltusotine or placebo, normal IGF-I levels were maintained over a period of 36 weeks in approximately 83% of the patients in the paltusotine group, as compared with only 3.6% of those in the placebo group.

Cabergoline, a dopamine receptor agonist approved as a highly effective drug for prolactinoma, has been used off label for oral treatment of acromegaly, since somatotrophs express D2 receptors. The doses used for acromegaly are generally

higher than those used for prolactinomas. However, cabergoline may control disease in 20 to 30% of patients with acromegaly, generally those with modest IGF-I elevations (up to 2 times the upper limit of the normal range) and those with adenomas that secrete both prolactin and growth hormone.[67] Therefore, this drug is now a viable option as monotherapy only in patients with mildly active acromegaly after surgical failure.[51]

Growth Hormone Antagonists

Pegvisomant is a pegylated growth hormone analogue with amino acid substitutions that result in a functional block of growth hormone receptor and hepatic production of IGF-I.[68] In clinical trials, daily subcutaneous pegvisomant injections as monotherapy led to biochemical control in approximately 90% of patients. On the basis of real-life data, however, IGF-I levels are normalized in approximately 70% of patients, a result that is probably due, at least in part, to reduced adherence and to the high cost of the drug, with consequent nonuniform availability.[69] Pegvisomant also improves glucose metabolism in patients with acromegaly.[69] Tumor growth during treatment with pegvisomant was reported as uncommon (occurring in approximately 3% of patients) in large observational studies with centralized MRI readings.[70] Lipodystrophy and increased liver enzyme levels are rare with pegvisomant, which is indicated in patients whose disease is not controlled or who have unacceptable side effects with either octreotide or lanreotide and for whom hyperglycemia (but not adenoma mass) is a relevant clinical issue. Such patients should be monitored with periodic MRI studies.[63] For patients in whom tissue expression of SSTR-2 and SSTR-5 is slow or absent, pegvisomant could be considered as first-line medical treatment.[63]

Combination Therapy

According to a recent international survey, approximately 30% of patients with acromegaly are receiving combination treatments.[71] For example, combining pegvisomant and somatostatin receptor ligands has a mechanistic rationale; may improve biochemical control, as compared with somatostatin receptor ligands alone; may reduce the dose, costs, and injection burden of pegvisomant monotherapy[72]; and is indicated when there are concerns about the adenoma mass and hyperglycemia.[63] Cabergoline can be combined with somatostatin receptor ligands or pegvisomant, which improves their efficacy, particularly in patients with tumors that also secrete prolactin.[50]

RADIOTHERAPY

Radiotherapy is generally a third-line treatment option, after the failure of surgical and medical therapy.[63] Conventional radiotherapy, which is associated with an increased risk of cerebrovascular and pituitary damage, is used for large target masses and is administered over a period of several weeks. Stereotactic radiosurgery, in a single administration with a gamma knife, is preferred for small tumors that do not impinge on the optic chiasm. Growth hormone and IGF-I levels may not fall into the normal range for a period of several years after radiotherapy, and late hypopituitarism may occur.[50]

REVERSIBILITY OF COMPLICATIONS AND QUALITY OF LIFE

Diagnostic delay and therapeutic inertia (failure to make changes in treatment when hormonal control is not achieved)[71] are two modifiable risk factors directly affecting the natural history and outcomes of acromegaly. With timely diagnosis and modifications in treatment to achieve hormonal control, the overall time during which IGF-I levels are elevated can be minimized sufficiently to reverse most of the manifestations of acromegaly and bring the risk of death down to that in the general population.

COMPLICATIONS AND QUALITY OF LIFE

Hypertension and left ventricular hypertrophy, sleep apnea, and arthropathy can be ameliorated, but they rarely disappear and may even progress, despite effective treatment. Vertebral fractures can also occur in patients with normal IGF-I levels. In contrast, hyperglycemia, carpal tunnel syndrome, and soft tissue hypertrophy may resolve when acromegaly is controlled, although medical treatment may have intrinsic dysglycemic effects. The risk of cancer appears to be decreased among patients with controlled disease.[31] This variability in the clinical response to normalized IGF-I levels is reflected by the persistence of a poor quality of life among patients with controlled acromegaly, particularly those receiving medical therapy.[73] Specific treatments

are needed for coexisting conditions that do not remit with normalization of IGF-I levels.[20]

MORTALITY

Data on survival among patients with acromegaly vary, depending on the country, health care system, length of follow-up, and number of cases studied. Findings published in recent years show lower mortality than that reported in the past, a difference that is probably due to improved treatment and implementation of global guidelines in pituitary tumor centers of excellence,[51] as well as to improved follow-up of coexisting conditions and use of disease-specific staging tools.[50] In fact, a recent analysis of data from the U.K. Acromegaly Register showed that a shorter time to remission, surgery, and use of somatostatin receptor ligands were associated with prolonged survival.[74] However, an increase in the standardized mortality rate due to oncologic and cardiovascular causes persists, at least in subpopulations defined by a diagnostic delay of more than 10 years (standardized mortality rate, 1.76),[10] older age (1.93), female sex (1.67), and diagnosis before 2008 (1.25).[75]

CONCLUSIONS

Diagnostic delay is a common denominator that determines the local and systemic manifestations of acromegaly, a progressive disease that nonspecialists tend to be unaware of because it is relatively rare and has an insidious onset. The condition still has a major adverse effect on the quality of life and on survival. The best screening test is an IGF-I assay, when appropriate. Improved scoring and AI systems for clinical screening and recognition of acromegaly facies, as well as more adequate information for both physicians and patients, should help reduce diagnostic delays.

Despite multimodal treatment, acromegaly is hard to control in some patients because of the biologic features of the tumor, poor adherence, ineffective treatment, side effects, or a combination of these factors, which may lead to a poor quality of life and increased mortality. Improved surgical techniques, wider availability of molecular profiling of tumors, new targeted drugs with increased efficacy and better adherence, and improved clinical monitoring during follow-up may ameliorate the outcome.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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