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Contemporary Management of Acromegaly: A Practical Approach

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Abstract

Acromegaly is a rare, chronic disease that is, in more than 95% of cases, caused by a growth hormone (GH)-secreting pituitary adenoma. Overproduction of insulin-like growth factor-1 (IGF-1) due to GH hypersecretion leads to various clinical features characterized by somatic overgrowth, physical changes, multiple comorbidities, and increased mortality. The average age at diagnosis is 40 to 50 years, with no sex predilection. The mean delay in diagnosis is 4.5 to 5 years due to the insidious onset and slow clinical progression of the disease. The diagnosis is confirmed by increased levels of IGF-1 and insuppressible GH measured by an oral glucose tolerance test. Treatment is aimed at normalizing GH/IGF-1 levels and controlling tumor volume. Medical treatment and radiotherapy can be utilized when surgery fails to control GH/IGF-1 hypersecretion. This article aims to review recent updates in acromegaly diagnosis and treatment to raise awareness about acromegaly clinical presentation and management.

Keywords
- acromegaly
- clinical features
- diagnosis
- mortality
- treatment
- surgery
- medical therapy
- radiotherapy
- outcome

Introduction

Acromegaly is a chronic disease characterized by excessive secretion of growth hormone (GH), mainly caused by a pituitary adenoma.[1] Acromegaly results in various clinical features ranging from subtle signs of acral overgrowth, soft tissue swelling, arthralgias, jaw prognathism, and hyperhidrosis to florid osteoarthritis, severe headache, sleep apnea, severe hypertension, respiratory and cardiac failure, and possibly neoplastic complications.[2,3] The diagnosis is usually confirmed biochemically, with elevated serum IGF-1 and a lack of GH suppression after oral glucose tolerance test (OGTT). Furthermore, pituitary magnetic resonance imaging (MRI) is recommended to identify an underlying pituitary adenoma.[4] The treatment aims to achieve an average IGF-1

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level for the patient's age and gender and normal concentrations of GH. Other treatment objectives include symptom relief, management of complications, and an improvement in the patient's quality of life.[5] Acromegaly is managed by surgical, pharmacological, and radiotherapeutic approaches.[4] Each treatment strategy has distinct benefits and disadvantages that should be carefully considered for each patient. Surgery is the primary therapy, with early remission rates of 75 to 90% for microadenomas and 40 to 60% for macroadenomas.[6] However, 40 to 60% of individuals may suffer from recurrent or persistent disease after surgery, needing further therapy.[7] Each treatment plan has its advantages and drawbacks that must be carefully considered for each patient.

Epidemiology

Acromegaly is a rare disorder with prevalence ranging from 2.8 to 13.7 cases per 100,000 individuals and incidence rates ranging from 0.2 to 1.1cases per 100,000 people per year.[8,9] While most published data come from European nations, data from other regions are limited.[8,10,11] Acromegaly is becoming more common in the twenty-first century. This could be because of the advancement of diagnostic tools and the increased awareness of the disease among healthcare providers.[12,13] The median age at diagnosis is 40.5 to 47 years (males: 36.5–48.5 and females: 38–56), although an increasing number of elderly patients (aged >65 years) are being diagnosed with acromegaly, and the average time between the appearance of the first symptom and the diagnosis is 4.5 to 5 years.[14–16] Both genders are affected equally. Males are diagnosed younger than females, with a median age difference of 4.5 years. As a result of this difference, women have a 2 to 4.6 year-long delay in diagnosis than men.[17] Younger patients have been reported to have more aggressive tumors and higher GH concentrations[18]

Approximately 99% of acromegaly patients have GH-secreting pituitary adenomas, whereas the other 1% have ectopic tumors that secrete growth hormone-releasing hormone (GHRH) or, more rarely, GH.[19] At the time of presentation, more than 70% of somatotroph adenomas are macroadenomas. While sporadic GH-secreting adenoma occurs in approximately 95% of acromegaly patients, familial syndromes account for the remainder of acromegaly cases. The most common familial syndrome is the multiple endocrine neoplasia type 1 syndrome, followed by the McCune-Albright syndrome, familial acromegaly, Carney's syndrome, and familial isolated pituitary adenoma.[18]

Pathophysiology

More than half of the hormone-secreting cells in the pituitary gland are somatotroph cells; these cells produce and store GH.[20] Integration of hypothalamic, dietary, hormonal, and intrapituitary signals determines GH secretion. Hypothalamic GHRH and gut-derived ghrelin stimulate GH synthesis and secretion, whereas hypothalamic somatotropin release–inhibiting factor inhibits GH secretion. The transcription factors paired-like homeodomain factor 1 and POU class 1 homeobox 1, affect cellular proliferation and GH production and secretion. IGF-1, the target polypeptide hormone for GH, is synthesized in the liver and extrahepatic tissues, mainly bone, muscle, kidney, and the pituitary gland. Most of GH's growth-promoting actions are mediated by IGF-1.[21] The most prevalent cause of acromegaly is an anterior pituitary somatotroph (GH-secreting) adenoma. The development of GH-secreting tumors results from unconstrained somatotroph proliferation coupled with intrinsic cell-cycle dysregulation and altered endocrine and/or paracrine mechanisms governing GH synthesis, GH secretion, and somatotroph cell growth.[5]

Several genes are implicated in the pathogenesis of somatotroph adenomas, including mutations of the alpha subunit of the guanine nucleotide stimulatory protein (Gs-alpha) gene, which has been present in around 40% of cases, and the less commonly encountered pituitary tumor transforming gene, which could potentially also predict the degree of tumor invasiveness.[22,23] The disease's clinicopathological spectrum varies from mild to severe and aggressive forms (►**Table 1**).[24]

Clinical Presentation

The clinical presentation of acromegaly is varied. It ranges from mild signs of somatic overgrowth, soft tissue swelling, arthritis, and hyperhidrosis to more severe signs and symptoms like facial and skeletal disfigurement, severe headache, sleep apnea, severe hypertension, diabetic ketoacidosis, florid osteoarthritis, respiratory, and heart failure (►**Table 2**).[5,25] These clinical manifestations can be attributed to the direct and indirect effects of high GH and GH-dependent IGF-1 and the local effects of a growing pituitary tumor.[25]

Even though the acromegaly features are distinctive and straightforward, they typically develop insidiously and slowly over a long time.[26,27]

The initial diagnosis is made by an internist or a family physician in 28.4 and 27.1% of cases, respectively. The remainder is diagnosed when another specialty sees patients for different reasons. For instance, an ophthalmologist may see patients for visual disturbances, a dentist for bite problems, a rheumatologist for osteoarthritis, a sleep disorder specialist for obstructive sleep apnea, or a gynecologist for menstrual dysfunction or infertility.[28] ►**Table 2** summarizes the most frequently reported symptoms and signs of acromegaly.

Comorbidities

Acromegaly patients usually have more comorbidities and need more medications than nonacromegaly patients.[29] In addition to biochemical monitoring and control, clinical screening, diagnosis, and individualized therapy for each comorbidity could improve patient outcomes.[3] Important factors determining a patient's comorbidities include GH & IGF-1 levels before and after treatment, age, tumor size, the extent of tumor invasion, and disease duration.[5]

Table 1 Clinicopathological spectrum of acromegaly

Subtype	Frequency	Clinical presentation	Pathology	Response to treatment
Densely granulated somatotroph tumor	30–50%	Usually present in patients older than 50 years Slow growing lesions High levels of GH and IGF-1, and florid and symptomatic presentation of acromegaly	Diffuse positivity for GH and a perinuclear staining pattern of low molecular weight keratins that closely resemble normal somatotrophs	Biochemical response with somatostatin analogs 65–90%
Sparsely granulated somatotroph tumor	15–35%	More common in patients <50; often present with a more rapidly growing tumor; larger at diagnosis compared to densely granulated tumors. GH and IGF-1 levels not as high as in densely granulated cases	Weak or focal positivity for GH and do not express the α-subunit more aggressive, with Ki67 proliferation indices >3% in most cases	Often resistant to treatment with somatostatin receptor ligands (SRLs)
Mammosomatotroph tumor		Similar to the densely granulated somatotroph tumors in addition to hyperprolactinemia	Express both GH and prolactin	Limited data likely that similar to densely granulated tumors
Mature plurihormonal Pit1-Lineage tumor		Almost identical to mammosomatotrophs; patients may also have hyperthyroidism.	Resemble mammosomatotroph tumors may synthesize and secrete TSH	
Mixed somatotroph-lactotroph tumor		Increased risk of invasion into surrounding structures,	Two distinct cell populations, somatotrophs, and lactotrophs	Low remission rate High recurrence rate 18.2%
Acidophil stem cell tumor	Rare	Usually present with hyperprolactinemia symptoms, while acromegaly is less frequent Mildly elevated GH and symptoms of hyperprolactinemia dominate the clinical picture (fugitive acromegaly)	Express mainly prolactin but also GH	Frequently invasive, fast-growing macrotumors Frequently resistant to dopamine agonists
Poorly differentiated Pit1-lineage tumor		Can produce different combinations of GH, prolactin, α-subunit and/or TSH. Usually macrotumors, and are more aggressive and invasive	Composed of poorly differentiated, polygonal to spindle-shaped chromophobic cells that express Pit1 as well as focally positive for ER & GATA3	High recurrence rate following surgery

Abbreviations: ER, estrogen receptor; GH, growth hormone; IGF-1, insulin-like growth factor-1; TSH, thyroid-stimulating hormone.

Neurology Complications

Extraseller tumor extension produces a direct compressive effect, causing headaches and visual field defects such as bitemporal hemianopsia and cranial nerve palsies. Headache and visual field defects were the presenting features in one study in 8 and 3% of the cases, respectively.[30] With the progression of the disease, headache and visual field defects are eventually reported in 60 and 10% of the cases, respectively.[5,31] In addition to carpal tunnel syndrome, which occurs in 18 to 84% of cases, acromegaly patients may develop peripheral symmetrical mixed sensory-motor neuropathy.[32,33] Proximal myopathy with myalgia, cramps, nonspecific electromyography changes, and muscle fiber hypertrophy may occur in 50% of the patients[34]

Skeletal Changes

Approximately 70% of patients have arthropathy characterized by joint swelling, synovitis, periarticular calcifications, thickening of cartilages, and hypermobility, whereas 50% of patients have limitations in their daily activities. It is possible to see a monoarticular or polyarticular pattern of joint involvement. Although tenderness, hypermobility, crepitus, and stiffness are common, joint effusions are rare.[35,36] Spinal involvement with osteophyte formation and disk space widening may cause kyphoscoliosis and fractures.[37] Acromegaly is associated with increased bone formation and resorption, resulting in increased bone density in both the spine and hip; however, bone density does not increase in estrogen-deficient women, and a higher incidence of vertebral fracture has been observed.[38]

Table 2 Local and systemic clinical manifestation of acromegaly

A. Local tumor effect	
Structural and functional local effects	Headache; visual impairment; cranial nerve palsy, hyperprolactinemia, hypopituitarism
B. The systemic effect of excessive GH/IGF-1	
Somatic features	Acral enlargement (excessive growth of hands and feet), prominence of the brow, furrowing of the front head, enlargement of the nose and the ears, thickening of the lips, facial skin wrinkles, nasolabial fold, prognathism, dental malocclusion, and increased interdental spacing
Skin	Increased skin thickness, hyperhidrosis, oily texture, skin tags, acanthosis nigricans
Cardiovascular	Hypertension, left ventricular hypertrophy, cardiomyopathy, congestive heart failure, arrhythmias
Musculoskeletal	Gigantism, prognathism, jaw malocclusion, increased articular cartilage thickness, arthralgias and arthritis, carpal tunnel syndrome, proximal myopathy, osteopenia
Neuropsychiatric features	Impaired self-esteem, body image distortion, disruption in interpersonal relations, social withdrawal, impaired cognition, anxiety, and depression
Respiratory	Sleep disturbances, excessive snoring, sleep apnea (obstructive and central), and narcolepsy
Metabolic	Insulin resistance, impaired glucose tolerance, diabetes mellitus, dyslipidemia, hypercalciuria, menstrual abnormalities, and sexual dysfunction
Neurological	Intracranial aneurysms, herniation of cerebellar tonsils, and pituitary apoplexy
Visceromegaly	Enlargement of organs such as tongue, thyroid, liver, spleen, kidney, prostate

Abbreviations: GH, growth hormone; IGF-1, insulin-like growth factor-1.

Cardiovascular Complications

Up to 60% of acromegaly patients have symptomatic cardiovascular disease, a significant cause of mortality and morbidity. Concentric biventricular hypertrophy is the most prevalent manifestation of acromegaly-related cardiomyopathy.[39,40] Cardiomyopathy comprises three stages. In the early hyperkinetic phase of young patients with short disease duration, initial cardiac hypertrophy, tachycardia, enhanced contractility, and high systolic output are seen. However, more established hypertrophy and diastolic and systolic dysfunction are observed in the subsequent phase. Systolic dysfunction and heart failure with dilated cardiomyopathy are associated with a longer duration of the disease or insufficient control of the GH/IGF-1 level in treated patients.[41] Heart failure is seen in 3 to 10% of the subjects, though around 25% harbor left ventricular dysfunction.[42] Valvular dysfunction may be detected in up to 75% of patients at the time of diagnosis.[43] Chronic GH/IGF-1 elevation is associated with regurgitation of the mitral and/or aortic valves in 5 and 30% of patients, respectively.[44]

Metabolic Complications

Both diabetes mellitus (DM) and impaired glucose tolerance are frequently associated with acromegaly. In different studies, the prevalence of DM ranges from 19 to 56%. Advancing age, higher GH levels, and disease duration are significant predictors of the development of DM.[45] Dyslipidemia affects up to 71% of patients.[3] Levels of plasma free fatty acids are elevated as lipolysis is induced by GH, and low HDL levels with hypertriglyceridemia are the primary abnormalities observed.[3,27] Glomerular hyperfiltration is characteristically observed with urinary albuminuria. IGF-1-mediated direct renal tubular absorption leads to hyperphosphatemia, while hypercalcemia along with hypercalciuria are other electrolyte abnormalities[46]

Respiratory Complications

Snoring was documented in 78% of cases, sleep apnea in 75%, fragmented sleep in 60%, daytime somnolence in 51%, and morning sleepiness in 16% of patients with acromegaly.[47] These disorders predispose to Coronary artery disease (CAD), arrhythmias, hypertension, and cerebrovascular accidents.[47] Approximately one-third of the patients suffer from central sleep apnea due to the direct effect of excess GH/IGF-1 on the breathing center or an increased somatostatin tone.[48] Obstructive sleep apnea is seen in more than 50% of the cases. It is mainly due to upper airway anatomical changes leading to obstruction, such as thick lips, prognathism, and hypertrophied laryngeal mucosa, leading to thickened true and false vocal cords, laryngeal stenosis, hypertrophied nasal structures, tracheal calcification, and arthropathy of the cricoarytenoid joint.

Endocrine Complications

An expanding adenoma causes hypopituitarism, but it may also occur secondary to pituitary surgery and radiotherapy, with a prevalence ranging from 16.6 to 37%.[15,49,50] The gonadal axis is the most affected pituitary axis, resulting in a deficiency of LH/FSH with a prevalence of around 53%. Menstrual disturbances, hot flashes, and vaginal dryness are common manifestations. Reduced testicular volume and facial hair, erectile dysfunction, and loss of libido are commonly encountered among affected men.[51] Secondary osteoporosis is due to hypogonadism and can occur in 12 to 32%

of the cases; despite average bone density, a higher fracture risk was observed.[38] Thyroid overgrowth may be diffuse or multinodular, and ultrasonography studies have shown a frequency of 92% and a mean thyroid volume of more than five times. Thyroid nodules increase with disease duration.[52] Hyperthyroidism occurs in 3.5 to 26% of cases, although toxic nodular goiter occurs in 14%.[53] Thyroid growth is independent of genetic, endemic, or dietary variables and is linked to disease duration, age, and IGF-1.[27]

Neoplasia

In one study, adenomatous were seen in 22% of patients and 8% of controls, and those with a male gender, age above 50 years, family history of colon cancer, and three or more skin tags were more likely to have polyps.[54] In one meta-analysis, the risk for adenoma and colon cancer was 2.5- and 4.4-folds higher, respectively, compared to the control.[55] Despite various observational studies suggesting the association between benign and malignant polyps and the increased prevalence of colonic neoplasia in acromegalic patients, a cause-effect relationship is yet to be proven.[56] Thyroid cancer, mainly papillary, affects 4% of people, according to a systematic review.[57]

Mortality

Patients with acromegaly have a greater risk of mortality than the normal population, as initially observed by Wright et al.[58] Data analyzing the risk of death since 2004 have shown a rise in mortality due to cardiovascular complications, reaching 40 to 60% of all cases of acromegaly, while deaths due to respiratory difficulties and malignancies accounted for 25 and 15% of all cases respectively.[27] Recently, mortality data have shifted, revealing an overall reduction in mortality among acromegaly patients. A standardized mortality rate (SMR) of 1.57 was reported in a comprehensive review and meta-analysis of mortality studies in acromegaly published in 2008.[59] Overall, the causes of mortality have shifted from 44% cardiovascular deaths and 28% cancer deaths in the preceding decade to 23% cardiovascular deaths and 35% cancer deaths during the following 20 years, with pancreatic cancer being the most common cancer type.[60] In the Swedish National Study, cardiovascular disease was the leading cause of death in patients with acromegaly, followed by malignancy.[61] Another study examined the natural history of acromegaly and found an increase in mortality with SMR 1.41 and a twofold increased risk of malignancy.[62] Patient age at diagnosis was an independent predictor for all-cause mortality with a hazard ratio of 1.1 (95% confidence interval [CI]: 1.08–1.13) with a significant p-value (<0.001).[60] Death rates within 10 years following an acromegaly diagnosis were higher in patients with acromegaly, 32%, compared to 27% of the controls.[60] Mortality from acromegaly has recently declined due to advances in treatment modalities. Medical treatment with somatostatin analogs has also significantly reduced the risk of death.[59] Biochemical disease control of GH and IGF-1 helps determine mortality risk; studies have shown that GH levels less than 2.5 ng/mL carry the same mortality risk as the general population.[63] The use of IGF-1 as a surrogate for mortality risk is inconclusive, as studies have found conflicting data. However, significant increases in IGF-1 indicate increased mortality.[64] From 1983 to 2013, in Sweden, the frequency of primary treatment with surgical intervention for acromegaly increased dramatically in addition to reducing hypopituitarism, this contributed to a reduction in mortality.[61] Another predictor of increased mortality was radiation therapy with a reported SMR of 34.25 (95% CI: 1.42–824.93, $p=0.030$), and cause of death related to cerebrovascular disease has been observed despite improvements in radiation techniques such as stereotactic radiation therapy or radiosurgery.[65–67] In a different series that included only patients who underwent surgery or received radiation therapy, mortality was significantly higher (SMR: 2.11; CI: 1.54–2.91).[68] Hypopituitarism is associated with an increased risk of death. Mortality is mainly associated with a corticotropin-releasing hormone deficiency, cardiovascular complications, and intake of more than 30 mg of hydrocortisone per day, with a relative risk of 1.7 (95% CI: 1.2–2.5; $p < 0.004$). However, there was no increased risk of death due to deficiencies in other pituitary hormones in patients with acromegaly.[69]

Diagnosis

Detection of acromegaly necessitates vigilance and attention since a delayed diagnosis is linked to significant morbidity and mortality.[68] Numerous articles have addressed the morphological identification of acromegaly using photograph analysis and machine learning techniques. According to Kong et al, the sensitivity of such techniques may approach 96%.[70,71] The diagnosis of acromegaly should be considered in individuals who have characteristic clinical symptoms and an increased IGF-1 level relative to age and gender refernce ranges. However, confirmation with an OGTT for acromegaly is still the gold standard confirmatory test.[72] Evaluation of IGF-1 is complex, as in pregnant ladies, patients on estrogen therapy, or adolescents; in such conditions, patients present with nonpathological elevations of IGF-1. Other conditions that might lower IGF-1 levels include liver and kidney diseases, hypothyroidism, malnutrition, and impaired glycemic control.[73] Rising GH level initially correlates proportionally with IGF-1, however beyond a certain limit it loses this characteristic, probable related to hepatic GH receptor saturation as underlying mechanism.[74] GH is affected by many physiological and pathological factors, making it too complex to be used solely in diagnosing acromegaly.[74,75] The oral glucose tolerance test for acromegaly OGTT with 75g has excellent sensitivity and specificity to help establish the diagnosis of acromegaly when the nadir GH is more than 1 ng/mL in most worldwide available assays and more than 0.4 ng/mL in ultrasensitive assays. A lower value can exclude the acromegaly diagnosis[72,76]

Despite the previous report about GH being affected by hyperglycemia, studies on relatively controlled patients with diabetes with glycated hemoglobin less than 8% have shown that OGTT can still be reliable and effective in diagnosing acromegaly. However, poor diabetes controls are still a

Table 3 Types, forms, and outcome of the various therapeutic modalities of acromegaly

Treatment	Type of therapy/dose	Biochemical control (efficacy)	Onset of response	Side effect
A. Medical therapy				
First-generation somatostatin receptor ligand	Octreotide LAR (10–40 mg IM monthly) Lanreotide (30 mg IM every 10–14 days); lanreotide gel (60–120 mg deep SC monthly)	50–80% (depending on primary vs. adjuvant therapy, dose escalation)	Rapid	Nausea, vomiting, diarrhea, constipation, abdominal pain, cholelithiasis/biliary sludge, bloating, bradycardia, fatigue, headache, alopecia, dysglycemia
	Oral octreotide (40–80 mg, twice daily)	65%	Rapid	Nausea, vomiting, diarrhea, dyspepsia, cholelithiasis, headaches, dizziness, dysglycemia
Second-generation somatostatin receptor ligand	Pasireotide LAR (40–60 mg IM monthly)	36%	Rapid	Same as for the first generation with more hyperglycemia
GH–receptor antagonist	Pegvisomant (10–40 mg SC daily)	76–97%	Rapid	Elevated liver enzymes, lipodystrophy, arthralgias
Dopamine Agonist	Cabergoline (1–4 mg orally weekly)	34% in mild acromegaly	Slow (weeks)	Nausea, dizziness, orthostatic hypotension, the high dose required
B. Surgery				
	Transsphenoidal resection	50–80%	Rapid	Hypopituitarism 10% Tumor persistence or recurrence, 6%; diabetes insipidus, 3%; local complications, 5%
C. Radiotherapy				
	Conventional or radiosurgery	40–60% in 5–10 years	Slow (years)	Hypopituitarism 50% Local nerve damage, second brain tumor, visual and CNS disorders, approximately 2% cerebrovascular risk

Abbreviations: CNS, central nervous system; GH, growth hormone; IM, intramuscular; LAR, long-acting release; SC, subcutaneous.

diagnostic dilemma for the interpretation of OGTT.[77] Although the GH daily profile may be useful, it has not been implemented in clinical practice. After biochemical confirmation of acromegaly, an MRI of the pituitary is the next best step in most clinical guidelines, as pituitary GH-secreting adenoma is the most common cause of acromegaly.[72] In situations where MRI is contraindicated, imaging through computed tomography (CT) scan of the sella is another radiographic modality that can be used. If there is no detectable finding of a pituitary adenoma, consider measuring the GHRH level to diagnose an ectopic source and additional imaging for localization.[78]

Management

Goals of Management

The goals of treatment should be to reduce tumor size and biochemical control, minimize morbidity, and normalize mortality to the normal population while retaining normal pituitary function (►**Table 3**). These objectives can be met through a stepwise therapeutic strategy based on surgery, radiotherapy, and/or medical treatment (►**Fig. 1**).

For most patients, surgical resection of the adenoma is the first-line treatment, which may result in immediate cure or remission, especially for microadenomas.[79] Typically, medical treatment is reserved for patients who do not achieve a surgical cure. In contrast, radiotherapy is indicated as a third-line treatment option in patients who do not respond adequately to medical therapy or have a large, invasive, or growing residual tumor.[79]

Surgery

Surgery is the first-line treatment for patients with GH-secreting pituitary adenomas. Remission following surgery is usually achieved in 75 to 90% of patients with microadenomas and 40 to 60% of patients with macroadenomas.[6] Although transsphenoidal expanded approaches have become the preferred surgical technique in most cases, a transcranial approach may be required for large tumors with extrasellar extension. Although the endoscopic technique may provide a wider field of view for complete adenoma excision, particularly for those that extend laterally towards the cavernous sinus, there is no conclusive evidence that the endoscopic approach is superior to the microscopic approach in terms of short- and long-term remission rates, recurrence, or complications.[72] Despite the scarcity of direct comparative studies, the experience of the pituitary surgeon remains the primary predictor of success.[72] In a patient with

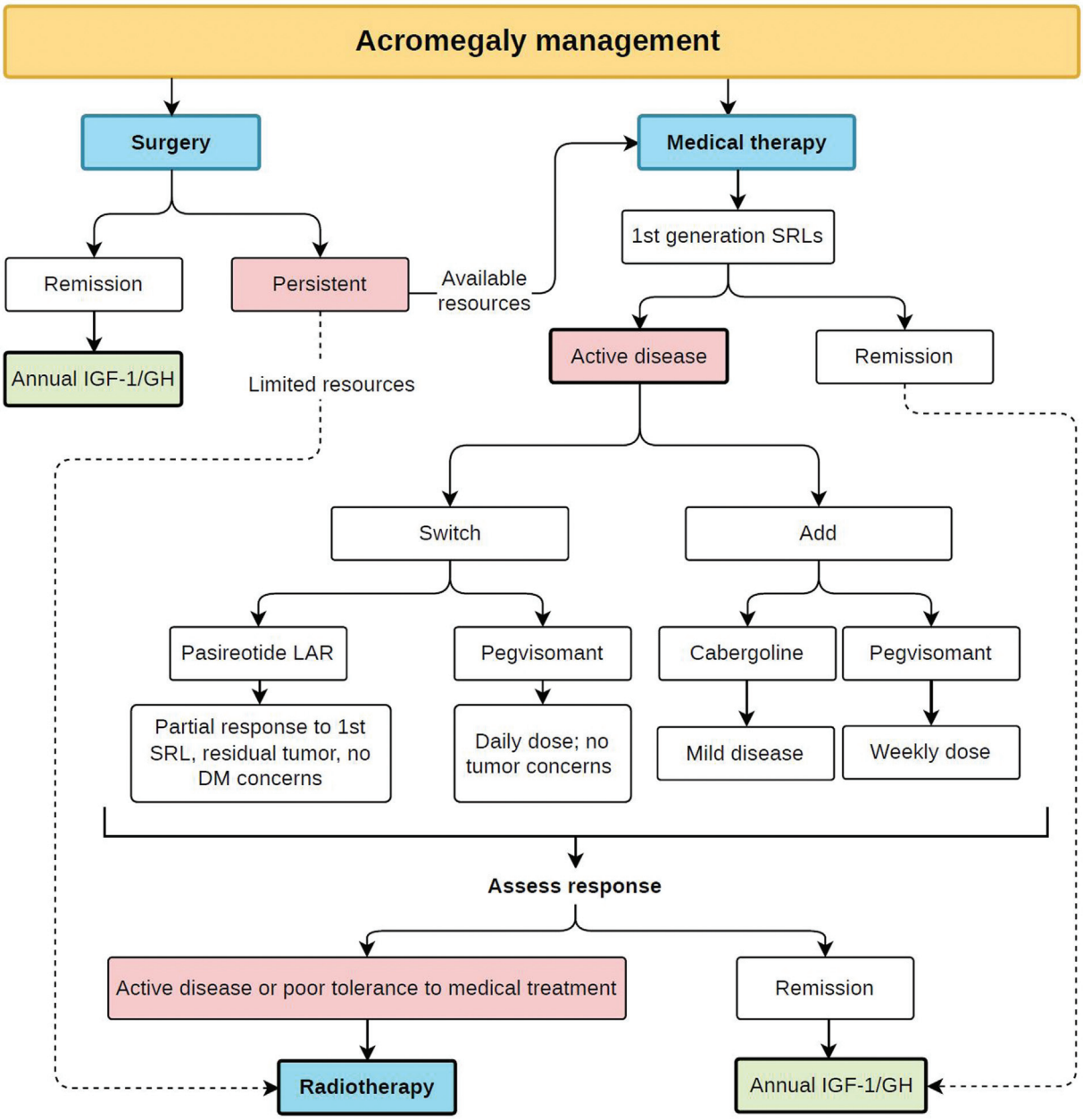

Fig. 1 Proposed approach to acromegaly management. GH, growth hormone; IGF-1, insulin-like growth factor-1; SRLs, somatostatin receptor ligands.

persistent disease after surgery, who did not achieve biochemical control despite medical therapy, or who has evidence of new tumor growth, reoperation might also be helpful when the tumor is accessible.[72] However, reoperation may be linked to a lower biochemical control rate compared to first-line surgery, particularly for macroadenomas and tumors invading the cavernous sinus. Furthermore, debulking pituitary surgery may result in a greater response rate to octreotide (OCT) than in those who received OCT as primary medical therapy.[80] The clinical outcome of surgery is measured in terms of its effectiveness in achieving "clinical remission" according to a universally agreed "consensus" criteria for biochemical remission, namely a random GH level of less than 1 µg/L and a GH nadir level post-OGTT less than 0.4 µg/L and a normalized level of IGF-1 for age and gender.[81] Success rates are affected by various factors, including tumor size, preoperative GH concentration, and surgeon experience.[72] The timing of measuring these parameters after surgery is not precise, and different groups have come up with early versus late predictors for achieving clinical remission. Hazer et al compared the outcome of early versus late predictive factors in 214 surgical cases of GH-secreting adenoma and showed that random GH levels less than 2.33 µg/L after the first day postoperatively and a more than 50% decrease in IGF-1 levels after the first month postoperatively could predict of cure.[82] In cases where biochemical markers fell short of the remission levels (GH nadir 0.4–1 µg/L, and MRI showing no residual), the authors advocated delaying starting medical therapy because, in these cases, remission can be achieved at the 1-year

follow-up. Similarly, in a series of 81 GH-secreting adenomas, Asha et al reported long-term follow-up data up to 100 months (±61), demonstrating a significant relapse rate of about 33% (early remission 73% dropped to 51%).[83] Interestingly, the authors identified two subgroups with discordant IGF-1/GH levels where patients might have achieved remission based only on one parameter, but the second remained high. Long-term follow-up revealed that patients with no evidence of residual disease on MRI are more likely to remain in clinical remission than patients with suspected residual disease on the postoperative MRI. These findings emphasize the significance of gross total resection in the first place as the most influential factor for long-term remission. The most significant predictive factor for surgical success appears to be the absence of cavernous sinus invasion (47.6% for patients with invasive macroadenomas and 76.4% for patients with noninvasive macroadenomas, (p.0.03)). The authors found no difference between microadenoma and macroadenoma in the absence of cavernous sinus invasion.[84] Negative predictive values are possessed by large size adenoma, highly elevated baseline GH and IGF-1, as well as evidence of prominent morphologic features of acromegaly at baseline, presence of cavernous sinus invasion, presence of extrasellar, suprasellar, or parasellar extension, and radiological Knosp grade 3-4.[83] In addition to patient-related predictive factors, surgical expertise is among the most important predictors advocating for managing these challenging cases in high-volume centers of excellence.[84,85]

Medical Therapy

First-generation somatostatin receptor ligands (SRLs; OCT, lanreotide autogel [LAN]) are first-line pharmacological treatments for acromegaly.[72] These injectable therapies, administered intramuscularly (OCT) or subcutaneously (LAN) every 4 weeks, are well tolerated and have comparable efficacy.[72] Biochemical control is expected in approximately 50-80% of patients depending on primary versus adjuvant therapy and dose escalation, and in approximately two-thirds of these patients, significant (>20%) tumor reductions were reported.[86] For patients well controlled on first-generation SRLs, switching to the oral formulation of OCT was associated with maintaining disease control in about 65 % of the patients with no significant adverse effects.[87] In addition, some patients who are controlled on first-generation SRLs every 4 weeks could maintain biochemical control with less frequent dosing of LAN 120 mg.[88]

Pasireotide is a second-generation SRLs with a broader affinity for somatostatin receptors, specifically somatostatin receptor 5 (SSTR5) and somatostatin receptor 2 (SSTR2).[89] Biochemical control is achieved in about 20% of cases, which are inadequately controlled with first-generation SRLs.[90] Hyperglycemia is an important factor limiting its wider use. However, pasireotide may be a better choice for patients with an inadequate response to first-generation SRL, low SSRT2 and high SST5 expression, T2 hyperintensity, significant residual tumor, sparsely granulated adenoma, or younger patients with aryl hydrocarbon receptor-interacting protein (AIP) mutations.[89]

Cabergoline (CAB) is a well-tolerated oral dopamine agonist administered twice weekly with excellent efficacy in prolactinoma.[91] CAB is not U.S. Food and Drug Administration-approved for acromegaly and is not commonly used as a monotherapy. A meta-analysis showed 52% normalization of IGF-1 when CAB was used as a combination therapy in patients uncontolled with SRLs.[92] Recently, in a similar cohort of patients inadequately controlled with first line SRLs, Sahin et al showed 58% IGF-1 normalization when CAB was added.[93]

Pegvisomant is a growth hormone receptor antagonist commonly used in patients inadequately controlled on SRLs.[72] It is highly effective in normalizing IGF-1 (76–97%), with disease control figures varying depending upon treatment dose and patients' heterogeneity.[94,95] Cost and availability are the main limiting factors for its use. Recent long-term data from ACROSTUDY, including more than 2000 patients from 15 countries, showed sustained treatment effects of pegvisomant (about 75% IGF-1 normalization at 10 years), low risk of liver enzyme abnormalities (3.2%), and a modest risk of tumor enlargement (7.1%).[96]

In clinical practice, many patients are uncontrolled on monotherapy and require switching to another drug or combination therapy. Factors influencing this decision include cost, availability, presence of diabetes/comorbidities, residual tumor size, and, most importantly, patient preference. A recent Italian study of 100 patients uncontrolled on first-generation SRLs showed that pasireotide long-acting release and pegvisomant monotherapy or in combination are effective and safe for the treatment of patient with invasive adenoma. Pasireotide was effective as a monotherapy for patients with a partial response to first-generation SRLs.[97]

Despite combination medical treatment, multiple surgeries, and radiotherapy, somatotroph adenomas can rarely be aggressive and resistant to multimodal therapy. In such a situation, chemotherapy with temozolomide could be used. In a recent case report, a 52-year-old woman with aggressive somatotroph adenoma continued to progress despite five surgeries, a combination of medical therapy, and stereotactic radiosurgery (SRS). The patient responded to a combination of temozolomide and capecitabine therapy with significant tumor shrinkage and reduction of GH and IGF-1 levels.[98]

Radiotherapy

Radiotherapy is usually the third-line treatment for tumors resistant to surgery and medical therapy.[99] The Acromegaly Consensus Group recommends radiation therapy for patients without postoperative biochemical response, large and unresectable tumors.[100] Radiation therapy is also suggested for individuals who have failed medical treatments or are at risk of tumor progression.[100] Therapeutic radiation for pituitary adenomas, including acromegaly, has advanced dramatically due to medical innovations and technological improvements. Conventional external beam radiation is the first such technique. Such treatment with a linear accelerator fractionates 40 to 45 Gy over 20 sessions.[101] Adenomas exceeding 3 cm and within 3 to 5 mm of the optic chiasm are treated with beam radiotherapy. The radiation exposure

may exceed the safe limit and damage nearby healthy tissues. CT/MRI-guided three-dimensional conformal radiation therapy has replaced conventional radiotherapy. Since the late 1980s, stereotactic radiotherapy delivered either by SRS or as fractionated stereotactic radiotherapy (FSRT) guided by CT and MRI images has been used. SRS gives high doses of radiation to a specific, focused region in a single session, whereas FSRT delivers lower doses across repeated sessions.[101] Essential SRS techniques include the use of photons—as in Gamma Knife radiosurgery, linear accelerator radiosurgery, and CyberKnife radiosurgery—or the use of protons.[102] The SRS offers a high dosage of radiation with submillimeter accuracy to a highly specified target without harming nearby healthy tissues and in less time than traditional radiotherapy. An early report from the 1990s suggested a consensus that pituitary irradiation after surgery produced a long-term drop in GH/IGF-I levels, with a long-lasting effect on pituitary function and tumor mass, achieving a target of less than 5 ng/ml of GH after 15 years among 90% of treated patients.[102] However, studies with recent state-of-the-art radiation technologies have demonstrated that they normalize hormone levels over time. Powell et al demonstrated normalization of IGF-1 levels in 69.2% of patients followed up 6 years after radiotherapy.[103] Biermasz et al showed even better results, with 84% of patients achieving IGF-1 level normalization after 15 years.[104] On a positive note, tumor growth was controlled in more than 90% of patients who underwent stereotactic radiotherapy as a primary treatment mode.[101] Conventional radiotherapy controls tumor volume in 80 to 100% of patients and normalizes GH/IGF-1 in 60 to 80% over 5 to 15 years due to the slow onset of beneficial effects.[105] The biochemical remission rate in radiosurgery is between 29 and 60%, with a follow-up period under 10 years in all studies and tumor growth control in more than 90% of patients.[103] Overall, SRS and conventional radiotherapy demonstrated similar biochemical and tumor growth control benefits. However, selection bias, tumor size, and duration of treatment all influence results. Furthermore, SRS has yielded fewer adverse effects on surrounding tissues. In short, strict definition criteria for disease control, the disparity in GH and IGF-1 levels following radiation treatment, and the availability of effective alternative treatments render a lower preference for radiotherapy in acromegaly management. Furthermore, hypopituitarism developed more frequently in SRS-treated patients, while adrenocorticotropic hormone and thyroid-stimulating hormone deficiency were common in those receiving FSRT. Ultimately, one-third of patients treated with either SRS or FSRT developed hypopituitarism during long-term follow-ups.[106] The Acromegaly Consensus recommends conventional radiotherapy for more extensive tumors close to the optic nerve. However, SRS is recommended for tumors distant from the optic apparatus to reduce radiation effects.[106] The primary adverse effect of SRS is radiation-induced hypopituitarism occurring in up to 66% of patients at a mean follow-up of 60.5 months. Nonetheless, individuals treated with FSRT had a 33% lower risk.[107] Other serious side effects, including radiation necrosis, carotid artery stenosis, and radiation-induced brain tumors, were observed in fewer than 1% of patients with a mean follow-up of 7 to 24 years.[108] Another follow-up study revealed a 1.7- to 2.8-fold greater risk for vascular damage, particularly among patients with hypopituitarism.

Conclusion

Acromegaly is a rare disease caused by GH hypersecretion, mainly from a pituitary adenoma. It is associated with significant morbidity and mortality, which requires early and tight disease control. Surgery remains the first line of treatment, particularly for microadenomas and well-defined intrasellar macroadenomas. However, complete biochemical and clinical remission is often challenging in patients with extensive and invasive macroadenomas with surgery alone. Medical treatment can be used, including SRLs, dopamine agonists, GH receptor antagonists, and/or radiotherapy. First-generation SRLs are generally preferred. However, the GH receptor antagonist (pegvisomant) is often used in patients resistant or intolerant to SRLs. More potent second-generation SRLs can achieve better biochemical and radiological control in patients who are resistant or intolerant to first-generation SRLs. Combination therapies of existing agents can provide biochemical and symptomatic disease control. Significant progress in the medical management of acromegaly and associated comorbidities improved the acromegaly outcome, allowing a life expectancy similar to that of the general population. To achieve such objectives, acromegaly management requires a multidisciplinary approach in all tertiary centers.

Authors' Contributions

The authors were assigned specific sections to draft, which were developed into a single manuscript reviewed and approved by all authors.

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Conflict of Interest

None declared.

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