Acromegaly: An Endocrine Society Clinical Practice Guideline

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Objective: The aim was to formulate clinical practice guidelines for acromegaly.

Participants: The Task Force included a chair selected by the Endocrine Society Clinical Guidelines Subcommittee (CGS), five experts in the field, and a methodologist. The authors received no corporate funding or remuneration. This guideline is cosponsored by the European Society of Endocrinology.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence. The Task Force reviewed primary evidence and commissioned two additional systematic reviews.

Consensus Process: One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of the Endocrine Society and the European Society of Endocrinology reviewed drafts of the guidelines.

Conclusions: Using an evidence-based approach, this acromegaly guideline addresses important clinical issues regarding the evaluation and management of acromegaly, including the appropriate biochemical assessment, a therapeutic algorithm, including use of medical monotherapy or combination therapy, and management during pregnancy. (***J Clin Endocrinol Metab*** **99: 3933–3951, 2014)**

Summary of Recommendations

1.0 Diagnosis

1.1 We recommend measurement of IGF-1 levels in patients with typical clinical manifestations of acromegaly, especially those with acral and facial features. (1|⊕⊕⊕◯)

1.2 We suggest the measurement of IGF-1 in patients without the typical manifestations of acromegaly, but who have several of these associated conditions: sleep apnea syndrome, type 2 diabetes mellitus, debilitating arthritis, carpal tunnel syndrome, hyperhidrosis, and hypertension. (2|⊕⊕◯◯)

1.3 We recommend measuring serum IGF-1 to rule out acromegaly in a patient with a pituitary mass. (1|⊕⊕⊕◯)

1.4 We recommend against relying on the use of random GH levels to diagnose acromegaly. (1|⊕⊕⊕◯)

1.5 In patients with elevated or equivocal serum IGF-1 levels, we recommend confirmation of the diagnosis by finding lack of suppression of GH to < 1 μg/L following documented hyperglycemia during an oral glucose load. (1|⊕⊕⊕◯)

1.6 Following biochemical diagnosis of acromegaly, we recommend performing an imaging study to visualize

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Abbreviations: CI, confidence interval; CT, computed tomography; LAR, long-acting release; MRI, magnetic resonance imaging; RT, radiotherapy; SRL, somatostatin receptor ligand; SRT, stereotactic RT; SST, somatostatin receptor subtype.

tumor size and appearance, as well as parasellar extent (1|⊕⊕⊕⊕). We suggest magnetic resonance imaging (MRI) as the imaging modality of choice, followed by computed tomography (CT) scan when MRI is contraindicated or unavailable. (2|⊕⊕◯◯)

1.7 We suggest performing formal visual field testing when the tumor is found to abut the optic chiasm on an imaging study. (2|⊕⊕⊕◯)

2.0 Presentation and management of comorbidities and mortality risk

2.1 We suggest evaluating all patients presenting with acromegaly for associated comorbidities, including hypertension, diabetes mellitus, cardiovascular disease, osteoarthritis, and sleep apnea. (2|⊕⊕◯◯)

2.2 We also recommend that such comorbidities be longitudinally monitored and rigorously managed. (Ungraded recommendation)

2.3 We suggest screening for colon neoplasia with colonoscopy at diagnosis. (2|⊕⊕◯◯)

2.4 We suggest a thyroid ultrasound if there is palpable thyroid nodularity. (2|⊕⊕◯◯)

2.5 We recommend assessing for hypopituitarism and replacing hormone deficits. (1|⊕⊕⊕◯)

3.0 Goals of management

3.1 We suggest a biochemical target goal of an age-normalized serum IGF-1 value, which signifies control of acromegaly. (2|⊕⊕◯◯)

3.2 We suggest using a random GH < 1.0 μg/L as a therapeutic goal, as this correlates with control of acromegaly. (2|⊕◯◯◯)

3.3 We suggest maintaining the same GH and IGF-1 assay in the same patient throughout management. (2|⊕⊕◯◯)

4.0 Surgery

Indications

4.1 We recommend transsphenoidal surgery as the primary therapy in most patients. (1|⊕⊕⊕◯)

4.2 We suggest that repeat surgery be considered in a patient with residual intrasellar disease following initial surgery. (2|⊕⊕◯◯)

Preoperative medical therapy

4.3 We suggest against the routine use of preoperative medical therapy to improve biochemical control after surgery. (2|⊕⊕◯◯)

4.4 For patients with severe pharyngeal thickness and sleep apnea, or high-output heart failure, we suggest medical therapy with somatostatin receptor ligands (SRLs) preoperatively to reduce surgical risk from severe comorbidities. (2|⊕◯◯◯)

Surgical debulking

4.5 In a patient with parasellar disease making total surgical resection unlikely, we suggest surgical debulking to improve subsequent response to medical therapy. (2|⊕⊕◯◯)

Postoperative testing

4.6 Following surgery, we suggest measuring an IGF-1 level and a random GH at 12 weeks or later (2|⊕⊕⊕◯). We also suggest measuring a nadir GH level after a glucose load in a patient with a GH greater than 1 μg/L. (2|⊕⊕⊕◯)

4.7 We recommend performing an imaging study at least 12 weeks after surgery to visualize residual tumor and adjacent structures (1|⊕⊕⊕◯). We suggest MRI as the imaging modality of choice followed by CT scan when MRI is contraindicated or unavailable. (2|⊕⊕◯◯)

5.0 Medical therapy

5.1 We recommend medical therapy in a patient with persistent disease following surgery. (1|⊕⊕⊕⊕)

5.2 In a patient with significant disease (ie, with moderate-to-severe signs and symptoms of GH excess and without local mass effects), we suggest use of either a SRL or pegvisomant as the initial adjuvant medical therapy. (2|⊕⊕◯◯)

5.3 In a patient with only modest elevations of serum IGF-1 and mild signs and symptoms of GH excess, we suggest a trial of a dopamine agonist, usually cabergoline, as the initial adjuvant medical therapy. (2|⊕⊕◯◯)

5.4 We suggest against routine abdominal ultrasound to monitor for gallstone disease in a patient receiving a SRL (2|⊕⊕◯◯). Ultrasound should be performed if the patient has signs and symptoms of gallstone disease. (2|⊕⊕◯◯)

5.5 We suggest serial imaging with MRI scan to evaluate tumor size in a patient receiving pegvisomant. (2|⊕⊕◯◯)

5.6 We suggest monitoring liver function tests monthly for the first 6 months and then every 6 months in a patient receiving pegvisomant, with consideration of discontinuation of pegvisomant if the transaminases are greater than 3-fold elevated. (2|⊕⊕◯◯)

5.7 We suggest addition of pegvisomant or cabergoline in a patient with inadequate response to an SRL. (2|⊕⊕◯◯)

5.8 We suggest use of an SRL as primary therapy in a patient who cannot be cured by surgery, has extensive cavernous sinus invasion, does not have chiasmal compression, or is a poor surgical candidate. (2|⊕⊕⊕◯)

6.0 Radiotherapy (RT)/Stereotactic Radiotherapy (SRT)

6.1 We suggest use of radiation therapy in the setting of residual tumor mass following surgery, and if medical therapy is unavailable, unsuccessful, or not tolerated. (2|⊕⊕◯◯)

6.2 We suggest use of stereotactic radiotherapy (SRT) over conventional radiation therapy in patients with acromegaly, unless the technique is not available, there is significant residual tumor burden, or the tumor is too close to the optic chiasm resulting in an exposure of more than 8 Gy. (2|⊕⊕◯◯)

6.3 To monitor the efficacy of radiation therapy, we recommend annual GH/IGF-1 reassessment following medication withdrawal. (1|⊕⊕⊕◯)

6.4 We recommend annual hormonal testing of patients following RT for hypopituitarism and other delayed radiation effects. (1|⊕⊕⊕⊕)

7.0 Special circumstances

Gigantism

7.1 In patients with the rare presentation of gigantism, we recommend the standard approaches to normalizing GH and IGF-1 hypersecretion as described elsewhere in this guideline. (1|⊕⊕⊕◯)

Pregnancy

7.2 We suggest discontinuing long-acting SRL formulations and pegvisomant approximately 2 months before attempts to conceive, with use of short-acting octreotide as necessary until conception. (2|⊕⊕◯◯)

7.3 During pregnancy, we recommend that acromegaly medical therapy be withheld and administered only for tumor and headache control. (1|⊕⊕◯◯)

7.4 During pregnancy, we suggest serial visual field testing in patients with macroadenomas. (2|⊕⊕⊕◯)

7.5 We suggest against monitoring GH and/or IGF-1 levels during pregnancy. (2|⊕⊕⊕◯)

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed the diagnosis and treatment of acromegaly a priority area in need of practice guidelines and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group, an international group with expertise in development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research evidence to develop the recommendations. The Task Force also used consistent language and graphic descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕◯◯◯ denotes very low quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each *recommendation* is a description of the *evidence* and the *values* that panelists considered in making the recommendation; in some instances, there are *remarks,* a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.

The Endocrine Society maintains a rigorous conflict-of-interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which are reviewed before the members are approved to serve on the Task Force and periodically during the development of the guideline. The conflict-of-interest forms are vetted by the CGS before the members are approved by the Society's Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflict of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline but they must have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined by remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (eg, stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial

benefits. Completed forms are available through the Endocrine Society office.

Funding for this guideline was derived solely from the Endocrine Society, and thus the Task Force received no funding or remuneration from commercial or other entities.

Acromegaly is a chronic disorder caused by GH hypersecretion. GH circulates and stimulates production of IGF-1 from the liver and systemic tissues; IGF-1 in large part mediates the somatic and metabolic effects of GH. Hypersecretion of GH leads to excess production of IGF-1, leading to a multisystem disease characterized by somatic overgrowth, multiple comorbidities, premature mortality, and physical disfigurement. A multidisciplinary approach is critical for the management of acromegaly (3, 4).

Pathophysiology

Over 95% of patients with acromegaly harbor a GH-secreting pituitary adenoma arising from somatotroph cells, leading to GH and IGF-1 hypersecretion (5). GH is synthesized and stored in somatotroph cells in response to inducing signals including hypothalamic GHRH. GH production is suppressed by somatostatin signaling primarily through the somatostatin receptor subtype (SST) 2 (6). Peripheral signals, including IGF-1, steroids, and paracrine growth factors, also regulate GH production (7). GH-secreting adenomas most commonly include densely or sparsely granulated somatotroph tumors. Sparsely granulated somatotroph tumors are more common in younger patients and are more aggressive, whereas densely granulated tumors are smaller and more biochemically active (8, 9). Less commonly encountered tumors include mixed tumors and mammosomatotroph cell adenomas that cosecrete GH and prolactin.

In less than 5% of cases, excess GHRH secretion from a hypothalamic tumor or a neuroendocrine tumor (usually from lung or pancreas origin) may lead to somatotroph hyperplasia and acromegaly (10). More rarely, ectopic GH production by an abdominal or hematopoietic tumor may cause acromegaly (11). Several genetic and cell cycle control factors underlie the pathogenesis of these benign monoclonal somatotroph adenomas (12). Hereditary conditions include multiple endocrine neoplasia 1, Carney complex, and McCune-Albright syndrome. Germline aryl hydrocarbon receptor interacting protein mutations have been described in familial acromegaly with more aggressive tumors (13).

1.0 Diagnosis

1.1 We recommend measurement of IGF-1 levels in patients with typical clinical manifestations of acromegaly, especially those with acral and facial features. (1|⊕⊕⊕◯)

1.2 We suggest the measurement of IGF-1 in patients without the typical manifestations of acromegaly, but who have several of these associated conditions: sleep apnea syndrome, type 2 diabetes mellitus, debilitating arthritis, carpal tunnel syndrome, hyperhidrosis, and hypertension. (2|⊕⊕◯◯)

Evidence

Biochemical screening is recommended for all patients presenting with clinical features of acromegaly (14–16). Measuring an IGF-1 level is recommended as the initial screen for acromegaly because it is a marker of integrated GH secretion (17). IGF-1 levels exhibit a log-linear relationship with GH levels (18). Circulating IGF-1 half-life is approximately 15 hours, and serum levels are relatively stable (19), but the presence of IGF-1 binding proteins extends the IGF-1 half-life significantly. A normal IGF-1 level effectively excludes the diagnosis of acromegaly. False positives for a diagnosis of acromegaly may occur in pregnancy and late-stage adolescence.

Importantly, falsely elevated, normal, or low IGF-1 values may be encountered with hepatic and renal failure, hypothyroidism, malnutrition, severe infection, and poorly controlled diabetes mellitus (20–22). Oral estrogens may render the liver less responsive to GH, resulting in lower IGF-1 levels. A finding of an elevated IGF-1 with normal GH values needs to be interpreted based on the clinical findings because this may reflect earlier disease (23).

Because over half of all new diagnoses are made by primary care physicians, internists, and gynecologists, physician awareness of the comorbidities of acromegaly is key to early diagnosis. Acromegaly is associated with multiple medical comorbidities, including type 2 diabetes mellitus, carpal tunnel syndrome, debilitating arthritis, hypertension, and sleep apnea. Appropriate testing may be considered when several such conditions are present (3). However, there is no compelling evidence supporting the value of biochemical screening (serum IGF-1 measurement) of large patient populations with these commonly encountered comorbidities (24).

Remarks

IGF-1 levels decrease with age following adolescence. Therefore, all levels must be assessed in relationship to age-appropriate normal values for the specific assay being used. There is significant interassay variability for measurement of IGF-1 that needs to be taken into account (25, 26). In fact, the diagnosis of acromegaly was inaccurately excluded in 30% of single samples assayed for IGF-1 in 23

different laboratories (27). It is important for the clinician to have knowledge of the specific assay used.

1.3 We recommend measuring serum IGF-1 to rule out acromegaly in a patient with a pituitary mass. (1|⊕⊕⊕◯)

Evidence

Pituitary incidentalomas may secrete any spectrum of anterior pituitary hormones, and GH hypersecretion may not be clinically apparent (28). A subset of patients present with few symptoms and minimal physical disease features yet may exhibit a pituitary tumor mass with elevated GH and IGF-1 levels (29).

1.4 We recommend against relying on the use of random GH levels to diagnose acromegaly. (1|⊕⊕⊕◯)

1.5 In patients with elevated or equivocal serum IGF-1 levels, we recommend confirmation of the diagnosis by finding lack of suppression of GH to < 1 μg/L following documented hyperglycemia during an oral glucose load. (1|⊕⊕⊕◯)

Evidence

Despite the use of international reference preparations of GH (30, 31), the commercially available immunoassays produce heterogeneous values, and results from one laboratory cannot be compared with findings from another (32, 33).

Although an elevated random GH level is suggestive of acromegaly, single random GH measurements are not usually recommended due to inherent episodic GH secretion from both normal and adenomatous pituitaries (34). A nadir serum GH level < 1 μg/L within 2 hours after 75 g of oral glucose usually excludes the diagnosis (14, 35). Mild GH hypersecretion, with random GH levels < 1 μg/L, may be associated with mildly elevated serum IGF-1 levels (23). Increasing age, female gender, obesity, and elevated body mass index may be associated with abnormal postglucose GH suppression, and there is a need to define normal ranges for these variables (32, 36).

Remarks

A nadir serum GH < 0.4 μg/L after an oral glucose load has been considered for establishing the diagnosis (37). However, although current GH assays have improved sensitivity (14, 38, 39), many assays do not have sufficient accuracy at GH levels < 1 μg/L, and we suggest that a cutoff GH < 1 μg/L after the glucose load is sufficient for excluding the diagnosis. It is important to measure glucose levels before and after an oral glucose load to verify that hyperglycemia has been achieved.

Serum GH measurements are also fraught with challenges, including the lack of uniform assay standardization, poor reproducibility between laboratories and assays, imprecise standards, and the lack of robust normal control values using sensitive immunometric assays (39). Basal GH levels correlate with multisample day curves and nadir GH levels after glucose load in most studies (40–42). However, these procedures are both time-consuming and cumbersome.

1.6 Following biochemical diagnosis of acromegaly, we recommend performing an imaging study to visualize tumor size and appearance, as well as parasellar extent (1|⊕⊕⊕⊕). We suggest MRI as the imaging modality of choice, followed by CT scan when MRI is contraindicated or unavailable. (2|⊕⊕◯◯)

Evidence

Pituitary MRI is recommended to ascertain tumor size, location, and invasiveness (43). Macroadenomas are detected in up to 77% of subjects (44). It is recommended that the MRI be performed with two-millimeter slices to diagnose small microadenomas. GH-secreting adenomas with a hypointense T2-weighted MRI signal (45) have been shown to exhibit enhanced SRL responsiveness (46). A CT scan is reserved for subjects with a contraindication to MRI.

Remarks

Rarely encountered, a patient with biochemically confirmed acromegaly with a normal pituitary gland on MRI scan might pose a diagnostic and therapeutic challenge. Although the tumor may be microscopic and not sufficiently visible on a routine MRI scan (47), further testing, including measurement of serum GHRH as well as imaging (eg, somatostatin receptor scintigraphy [eg, octreoscan] and thoracic and abdominal imaging) may be considered to evaluate for ectopic disease (48).

1.7 We suggest performing formal visual field testing when the tumor is found to abut the optic chiasm on an imaging study. (2|⊕⊕⊕◯)

Evidence

Visual impairment due to optic nerve compression by the tumor dictates the choice and rapidity of treatment. Visual field testing is recommended to monitor lesions that abut the optic chiasm. Less frequently, tumor involvement in the cavernous sinus can produce other cranial nerve dysfunction leading to diplopia, blurred vision, and sensory changes (49).

2.0 Presentation and management of comorbidities and mortality risk

2.1 We suggest evaluating all patients presenting with acromegaly for associated comorbidities, including hyper-

tension, diabetes mellitus, cardiovascular disease, osteoarthritis, and sleep apnea. (2|⊕⊕◯◯)

2.2 We also recommend that such comorbidities be longitudinally monitored and rigorously managed. (Ungraded recommendation)

2.3 We suggest screening for colon neoplasia with colonoscopy at diagnosis. (2|⊕⊕◯◯)

2.4 We suggest a thyroid ultrasound if there is palpable thyroid nodularity. (2|⊕⊕◯◯)

Evidence

Morbidity and mortality from acromegaly are consequences of tumor compression, GH/IGF-1 excess, and secondary effects related to treatment (35, 50). There is an approximate 2-fold excess mortality in acromegaly due to the presence of diabetes, hypertension, and cardiovascular, cerebrovascular, respiratory, and some malignancy-related conditions (38, 51–53). Increased mortality rates are reported in patients who have undergone RT in some studies, and the presence of comorbidities including diabetes mellitus and hypertension may contribute as well (38, 51).

The prevalence of hypertension, insulin resistance, dyslipidemia, hypertrophic cardiomyopathy, and endothelial dysfunction is increased; however, the prevalence of coronary artery disease in acromegaly is unclear (54). GH hypersecretion increases insulin resistance, producing impaired glucose tolerance and diabetes mellitus in 15–38% of patients (44, 55–57). Hypertension occurs in 33–46%, with a predominance of diastolic blood pressure elevation that increases in prevalence with age (44, 55, 56, 58). Lipid patterns in acromegaly include elevated triglyceride and lipoprotein (a) levels and an excess of small, dense low-density lipoproteins (50, 59). Valvular heart disease, particularly aortic or mitral regurgitation, arrhythmias, and conduction disorders are frequent. Control of GH/IGF-1 excess during the early stages of disease is more likely to improve cardiomyopathy, but is unlikely to reverse hypertension or valvulopathy (50). The role of pretreatment echocardiography has not been defined; however, in the setting of suggestive clinical findings, particularly in perioperative patients, a thorough cardiac evaluation may be indicated. Because cardiovascular and cerebrovascular events are the primary cause of death in acromegaly, risk factors should be optimized by aggressive treatment of hypertension, diabetes mellitus, hyperlipidemia, and heart failure, and by smoking cessation and diet and exercise behavioral modification.

Sleep apnea syndrome is frequent in active acromegaly, with a prevalence of approximately 69%; it is primarily obstructive due to soft tissue thickening and edema of the tongue, pharynx, and upper airways, and less frequently due to a central sleep apnea mechanism (60). Although lowering GH/IGF-1 improves sleep apnea severity, up to 40% of those with controlled acromegaly have persistent sleep apnea, and initiation or titration of positive airway pressure treatment may be necessary (60–62).

The impact of acromegaly and its control on neoplasia risk and mortality is controversial (63, 64). A meta-analysis of studies has shown that the risk of colonic polyps is increased in acromegaly (65), although the true risk is unknown. Colonic screening in acromegaly may be challenging due to redundant, tortuous bowel and the presence of proximal colonic lesions. The timing of initial colonoscopy is controversial; a colonoscopy at diagnosis has been suggested, because up to 19.3% of acromegalic subjects less than 40 years old vs 4.4% of controls have been shown to have colonic neoplasia (66). After treatment, repeat colonoscopy is suggested every 5 years in those found to have a polyp or with persistently elevated IGF-1 and every 10 years in those without a polyp and with normal IGF-1 (67).

Acromegaly is associated with an increase in thyroid volume and nodularity. Disease duration correlates with the number of nodules on palpation (68). In multicenter studies, 54% of subjects had thyroid nodules (approximately 25% with toxic nodules), 18–20% with diffuse goiter, and 1.2–7.2% with thyroid cancer (> 1-cm papillary thyroid carcinomas) (69–73). Thyroid cancer is one of the more commonly detected cancers in acromegaly (69). In addition, a recent meta-analysis demonstrated further the high rate of thyroid nodules and thyroid cancer in acromegaly (74). These studies indicate the need for surveillance for thyroid disease in such patients. The prevalence of breast cancer and prostate cancer is not higher in acromegaly, although cancer-related mortality may be increased (64, 70).

Headache is reported in approximately 55% of subjects, and likely reflects tumor growth with stretching of the dura mater, cavernous sinus invasion with trigeminal nerve irritation, or GH hypersecretion itself (71). Excessive perspiration and seborrhea occur in up to 80% of subjects (72). Fatigue and weakness are also common symptoms.

Musculoskeletal changes and arthropathy are frequent and are due to cartilage hypertrophy, tendon laxity, and osteophyte development, followed by joint destruction. During long-term follow-up, joint complaints persisted in 77% of those with biochemical remission and negatively impacted quality of life (75). Early intervention with GH/IGF-1 control provides the best means to ameliorate arthropathy progression, with later stage disease requiring physical therapy, analgesia, and joint replacement.

Acromegaly may be associated with an increased risk of vertebral compression fractures despite normal bone density, and fracture risk may be accelerated by hypogonadism (76). Gonadal steroid replacement is important because hypogonadism contributes to loss of bone mineral density (77, 78). Maxillary and mandibular overgrowth can lead to painful jaw malocclusion requiring maxillofacial reconstruction. It is important to hold off on such reconstruction until GH/IGF-1 levels are stable because overgrowth may persist in the uncontrolled state. Peripheral neuropathies with sensory disturbances in hands and feet are frequently present, with carpal tunnel syndrome in 20–64% (79, 80).

Psychological changes, including alterations in personality due to impaired self-esteem, body image distortion, disruption in interpersonal relations, and social withdrawal, as well as anxiety and depression, are problematic in some patients (81, 82).

2.5 We recommend assessing for hypopituitarism and replacing hormone deficits. (1|⊕⊕⊕◯)

Evidence

Hypopituitarism may be due to tumor compression or a result of surgical or radiation treatment (83, 84). Adequate replacement of central adrenal, gonadal, and thyroid insufficiency is recommended. Hyperprolactinemia from tumor cosecretion (73, 85) or stalk effect can contribute to hypogonadism in acromegaly (86).

3.0 Goals of management

Two systematic reviews and meta-analyses were commissioned by The Endocrine Society. The first compared surgery and medical treatment in treatment-naive patients with acromegaly (87). It included 35 noncomparative studies. Compared with medical treatment, surgery had a higher remission rate (0.66; 95% confidence interval [CI], 0.60, 0.73; vs 0.45; 95% CI, 0.32, 0.63). The quality of this evidence was low considering the noncomparative nature of the studies, heterogeneity, and imprecision.

The second review included 31 noncomparative studies. Compared with conventional, fractionated radiation therapy, SRT was associated with a trend for higher remission rate (0.53; 95% CI, 0.41, 0.65) and lower rates of complications (panhypopituitarism, hypothyroidism, and hypoadrenalism) (87). The quality of this evidence was low considering the noncomparative nature of the studies, heterogeneity, and imprecision.

Based on these evidence synthesis summaries and the Task Force's own review of the individual studies, an algorithm for integrated multidisciplinary therapeutic approach was developed to aid practitioners in the care of patients with acromegaly (Figure 1).

3.1 We suggest a biochemical target goal of an age-normalized serum IGF-1 value, which signifies control of acromegaly. (2|⊕⊕◯◯)

3.2 We suggest using a random GH < 1.0 μg/L as a therapeutic goal, as this correlates with control of acromegaly. (2|⊕◯◯◯)

3.3 We suggest maintaining the same GH and IGF-1 assay in the same patient throughout management. (2|⊕⊕◯◯)

Evidence

Because of the variable nature of the disorder, an individualized treatment strategy is necessary. Goals of treatment are biochemical normalization, reduction of mortality risk, attenuation of symptoms, control of tumor mass, and maintenance of pituitary function.

An important caveat to consider is a lack of consensus for target GH and IGF-1 levels that correlate with prevention of comorbidities or reversal of mortality risk. IGF-1 levels correlate with comorbidities better than glucose-suppressed GH levels (88, 89). IGF-1 levels may be more predictive than nadir GH for predicting insulin sensitivity and clinical symptom score after surgery (88). A target GH < 1 μg/L and normalized IGF-1 values have each been shown to correlate with mortality risk reduction (90–92). Given the variability between GH and IGF-1 assays, it is critical to maintain the use of the same assay in the same patient if possible throughout management (32, 33, 93).

4.0 Surgery

Indications

4.1 We recommend transsphenoidal surgery as the primary therapy in most patients. (1|⊕⊕⊕◯)

Evidence

The favored surgical approach is via the transsphenoidal route, using either the operating microscope or the operating endoscope, along with microsurgical technique (94, 95). There is no definitive evidence of superiority of the endoscopic vs the microscopic approach with regard to short- and long-term remission rates, recurrence, or complications. The experience of the pituitary surgeon is the major determinant in achieving successful outcomes (96, 97). A multidisciplinary team is important for achieving optimal outcomes.

Successful surgery produces immediate lowering of GH levels and provides tumor tissue for pathological characterization (98, 99). Therefore, we recommend surgery as the primary therapy in most patients (100, 101).

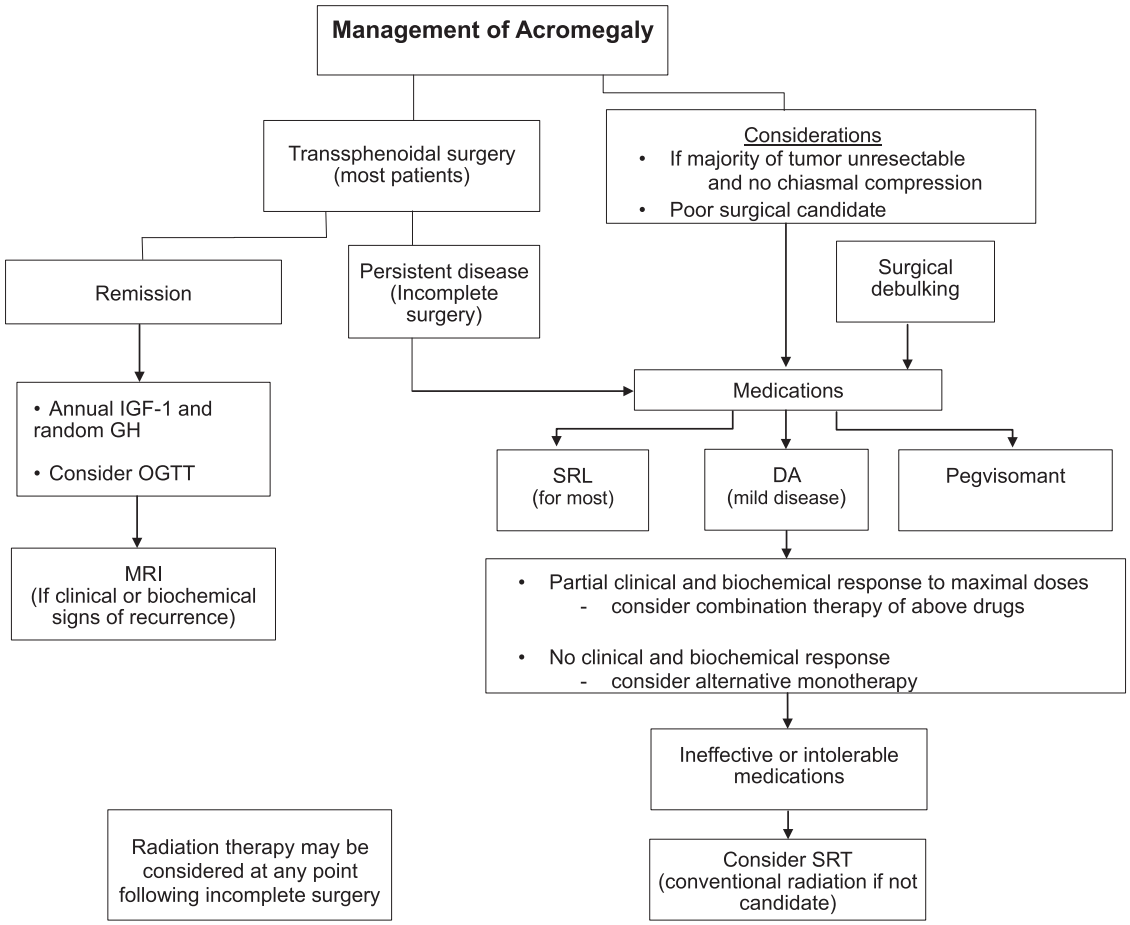

Figure 1. Treatment considerations in the approach to a patient with acromegaly. This approach refers to management of a patient with a pituitary adenoma. DA, dopamine agonist; OGTT, oral glucose tolerance test.

Complications from surgery include bleeding, spinal fluid leak, meningitis, sodium and water imbalance, and hypopituitarism (94, 99, 102, 103). Major complications such as carotid artery injury and visual loss are rare (102). Because of hypertrophic upper airway structures, fiberoptic intubation may be necessary, and careful perioperative airway management is essential (99, 104).

Pathology is useful to categorize the tumor further, including investigation of tumor aggressiveness (such as with Ki-67 index), presence of dural invasion, degree of granulation, or atypical appearance of the cells (105–107).

Outcomes of surgical management

With experienced pituitary surgeons, microscopic or endoscopic transsphenoidal microsurgery results in an initial remission rate > 85% for microadenomas and 40–50% for macroadenomas (94, 95, 108). Cavernous sinus invasion indicates tumor that is likely surgically unresectable (103, 109). Five-year disease recurrence rates range from 2 to 8% (94, 103, 108).

4.2 We suggest that repeat surgery be considered in a patient with residual intrasellar disease following initial surgery. (2|⊕⊕◯◯)

Evidence

In a patient with persistent disease after surgery, repeat surgery may be useful when the tumor is accessible (ie, not invading the cavernous sinus). In a recent study, repeat surgery was performed in 14 subjects who had failed initial surgery (110). Of these, 57% achieved biochemical control. This suggests a potential role of repeat surgery by an experienced surgeon (111).

Preoperative medical therapy

4.3 We suggest against the routine use of preoperative medical therapy to improve biochemical control after surgery. (2|⊕⊕◯◯)

Evidence

Three controlled prospective studies showed that up to 6 months of preoperative SRLs resulted in improved surgical outcomes in patients with macroadenomas (112–114). It should be noted that the improved surgical outcomes may have been exaggerated due to a carryover effect of the preoperative SRL on the 12-week postoperative IGF-1 levels. Therefore, there is a need for adequately controlled trial results before advocating such use.

4.4 For patients with severe pharyngeal thickness and sleep apnea, or high-output heart failure, we suggest medical therapy with SRLs preoperatively to reduce surgical risk from severe comorbidities. (2|⊕○○○)

Evidence

There is an increased risk of anesthetic complications including difficulty with intubation due to laryngeal and pharyngeal soft tissue and vocal cord swelling (115, 116). Oropharyngeal swelling and macroglossia result in sleep apnea syndrome, which may complicate both the pre- and postoperative status of the patient and delay extubation. Treatment with SRLs may reduce soft tissue swelling rapidly, with improved sleep apnea and reduced intubation-related complications (117). A role for preoperative SRL may be considered in a patient with severe pharyngeal thickness and sleep apnea syndrome.

Rarely, newly diagnosed patients present with high-output heart failure (118). Patients also have an increased prevalence of ventricular dysrhythmias (119). Treatment with SRLs in such patients improves cardiac function and may enhance anesthetic safety, and therefore may be considered in selected patients (119, 120).

Surgical debulking

4.5 In a patient with parasellar disease making total surgical resection unlikely, we suggest surgical debulking to improve subsequent response to medical therapy. (2|⊕⊕○○)

Evidence

In a patient with a macroadenoma with low likelihood of surgical cure due to extrasellar extension and no evidence of local compressive mass effects, surgical debulking to enhance subsequent medical therapy can be considered. Surgical debulking beneficially affects outcome and response to SRL (31, 109, 121, 122). In a prospective study (31), there was improved GH and IGF-1 response to lanreotide from 31 to 69% and from 42 to 89%, respectively, before and after surgical debulking. This suggests a role of surgical debulking to enhance response to medical therapy, particularly in a patient with highly active disease.

Postoperative testing

4.6 Following surgery, we suggest measuring an IGF-1 level and a random GH at 12 weeks or later (2/⊕⊕⊕○). We also suggest measuring a nadir GH level after a glucose load in a patient with a GH greater than 1 μg/L. (2|⊕⊕⊕○)

Evidence

Although GH testing may be performed as early as postoperative day 1, the role of an immediate postoperative GH value may be limited because an elevated value may reflect surgical stress with normal somatotroph GH production (123). The decline in IGF-1 is more delayed compared with GH, likely due to differential half-life of IGF-binding proteins. IGF-1 levels measured at 12 weeks after surgery are a valid reflection of surgical remission (124, 125). If the IGF-1 level has declined but is still not normal, measurement of a repeat IGF-1 level is warranted due to variability in the IGF-1 assay. A serum GH < 0.14 μg/L suggests "surgical remission," and a level < 1 μg/L indicates "control" and normalization of the mortality risk (126).

4.7 We recommend performing an imaging study at least 12 weeks after surgery to visualize residual tumor and adjacent structures (1|⊕⊕⊕○). We suggest MRI as the imaging modality of choice followed by CT scan when MRI is contraindicated or unavailable. (2|⊕⊕○○)

Evidence

Postoperative imaging should be performed no sooner than 12 weeks after surgery to allow for involution of gel foam and fat packing (127). This serves as the new baseline image for follow-up assessment. In patients with preoperative visual field defects, repeat visual field testing should be performed (128). In some patients, the visual field deficits continue to improve up to 1 year after surgery (123).

Values and preferences

A normal IGF value and undetectable GH value are sufficient for indicating surgical remission. However, if the GH is detectable (ie, >0.4 μg/L), measurement of GH after a glucose load may yield important information. We recognize that this may require a follow-up visit that may be cumbersome, so it may be time efficient to perform the oral glucose load at the same time as the IGF-1 measurement.

5.0 Medical Therapy

5.1 We recommend medical therapy in a patient with persistent disease following surgery. (1|⊕⊕⊕⊕)

5.2 In a patient with significant disease (ie, with moderate-to-severe signs and symptoms of GH excess and without local mass effects), we suggest use of either a SRL or pegvisomant as the initial adjuvant medical therapy. (2|⊕⊕○○)

5.3 In a patient with only modest elevations of serum IGF-1 and mild signs and symptoms of GH excess, we suggest a trial of a dopamine agonist, usually cabergoline, as the initial adjuvant medical therapy. (2|⊕⊕○○)

Evidence

If the biochemical and clinical evaluation after surgery reveals persistent disease, then adjuvant therapy is necessary. Medical therapy is initiated for disease control.

Somatostatin receptor ligands (SRLs)

There are two equally effective long-acting available preparations: im octreotide long-acting release (LAR), and deep sc lanreotide depot/autogel (128–131). These are usually administered monthly. Lanreotide depot/autogel may be self- or partner-injected (130, 131). The approved starting octreotide LAR dose is 20 mg monthly, with dose titration every 3–6 months down to 10 mg or up to 40 mg monthly. For lanreotide autogel/depot, the approved starting dose is 90 mg monthly, with dose titrations down to 60 mg or up to 120 mg monthly. The lanreotide autogel/depot 120-mg dose may be administered in up to 8-week intervals depending on biochemical response (132). Rapid-acting sc octreotide is also available. Effectiveness of treatment is based on measurement of serum IGF-1 and GH, which should be measured after 12 weeks just prior to the next dose. The utility of glucose-suppressed GH values during treatment with SRLs is not clear and is likely not helpful (36).

Determinants of SRL responsiveness. Tissue SST2 expression correlates with SRL responsiveness, but SST assessments are not routinely performed on tumor tissue (133). Smaller tumors and lower baseline GH and IGF-1 levels are important predictors of response (134, 135). Based on pathology analysis, densely granulated tumors are more SRL responsive than the more common sparsely granulated adenomas (8, 9). Hypointense T2-weighted tumor MRI images, which correlate with dense tumor granularity, portend a favorable SRL response (46). Additionally, we do not recommend performance of somatostatin receptor scintigraphy or an acute GH response to a sc octreotide injection as a determinant of SRL response because they are not routinely helpful (93, 136).

Responses to SRLs. Arthralgias, hyperhidrosis, soft tissue swelling, and headache frequently improve with SRL (137). SRLs may provide headache relief through direct mechanisms beyond those of GH suppression and tumor size reduction (138). IGF-1 normalization achieved by a SRL in both drug-naive and postoperative patients is approximately 17–35% (139–142). The recent analysis of the UK Acromegaly Database has shown similar figures (135). Prior studies that showed higher biochemical control rates reflected patient heterogeneity, differences in protocol length, and inclusion of patients preselected for GH responsiveness (128). In 59% of patients, SRL reduces tumor volume by more than 50% (143), and tumor shrinkage usually correlates with hormonal control (143).

Higher dose therapy may improve efficacy (144), and there are reports of improved efficacy with octreotide LAR doses up to 60 mg/mo and lanreotide autogel up to 180 mg/ mo. In patients who respond well to low-dose SRL therapy, treatment intervals may be lengthened (145).

Side effects. Abdominal cramps, flatulence, and diarrhea are common and usually abate with continued treatment. Side effects also include occasional local skin irritation and pain at the injection site. Less common are reversible hair loss and, rarely, alopecia. Because SRLs may inhibit both insulin and glucagon as well as GH secretion, glucose control usually improves but rarely may worsen (146).

5.4 We suggest against routine abdominal ultrasound to monitor for gallstone disease in a patient receiving a SRL (2|⊕⊕◯◯). Ultrasound should be performed if the patient has signs and symptoms of gallstone disease. (2|⊕⊕◯◯)

Evidence

Gallbladder stones and sludge occur in approximately 25% of subjects and are usually asymptomatic. In a recent study, only 4% of subjects with gallstone disease had biochemical evidence of cholestasis (147). Given the infrequent occurrence of symptomatic gallbladder disease, monitoring with gallbladder ultrasound is not considered necessary. Symptoms of gallbladder obstruction may occur after cessation of the SRL (148).

Remarks

Pasireotide is a novel SRL that has enhanced binding to more SSTs and has been shown to normalize IGF-1 in 35% of patients in a phase 3 trial (140). In addition to side effects that are similar to those of octreotide and lanreotide, pasireotide is associated with hyperglycemia in 57% of subjects (140). An oral preparation of octreotide has also been recently developed and has been tested in healthy volunteers (149). Trials are under way to evaluate the efficacy of an oral octreotide in acromegaly.

Pegvisomant

Pegvisomant, a human GH receptor antagonist, competes with endogenous GH for binding at its receptor and blocks peripheral production of IGF-1 (150–152). The antagonist does not target the GH-secreting pituitary tumor, and GH hypersecretion persists during drug administration (153).

Pegvisomant is administered sc as 10-, 15-, or 20-mg daily injections. In pivotal trials (154, 155), dose-dependent normalization of IGF-1 levels was achieved in up to 95% of patients receiving up to 40 mg daily. In the most recently published surveillance study involving 1288 patients, IGF-1 was controlled in 63% of patients (156). These efficacy discrepancies likely reflect "real life" compliance challenges as well as inadequate dose titration as

compared with a controlled trial environment. Recent trials indicate efficacy of using once or twice a week dosing, although this is mostly used when pegvisomant is combined with a SRL (see *Section 5.7*) (157). IGF-1 measurement is recommended as the effective biomarker of drug efficacy. GH levels should not be measured as a marker of efficacy with pegvisomant because GH hypersecretion persists and because of interference of pegvisomant in commercially available GH assays. As pegvisomant exhibits a favorable benefit for glycemic control, this medication may be useful when comorbid diabetes mellitus is present with acromegaly (158).

5.5 We suggest serial imaging with MRI scan to evaluate tumor size in a patient receiving pegvisomant. (2|⊕⊕◯◯)

Evidence

Tumor growth may occur in 3–5% of patients, but it is unclear whether this is due to the tumor natural history or to decreased negative feedback by the lower IGF-1 levels (159, 160). Because pegvisomant does not have a tumor-suppressive effect, we suggest serial imaging at 6 and 12 months after treatment initiation (161). If there is no size change at 1 year, then yearly imaging is suggested. In a patient with a large tumor abutting the optic chiasm and vital central structures, we suggest that alternative tumor-targeted medical therapies be considered (162).

Side effects

Injection site reactions have been reported in 2.2% of patients and include local discomfort, reversible lipohypertrophy, or lipoatrophy (163).

5.6 We suggest monitoring liver function tests monthly for the first 6 months and then every 6 months in a patient receiving pegvisomant, with consideration of discontinuation of pegvisomant if the transaminases are greater than 3-fold elevated. (2|⊕⊕◯◯)

Evidence

In the German Observation Study, pegvisomant administration was associated with a rise in liver enzymes in 9% of subjects (164). In a recent observational study involving 1178 subjects with available tests, 30 (2.5%) had an elevated aspartate aminotransferase or alanine aminotransferase reported greater than three times the upper level of normal (156). Based on these data, liver function should be monitored serially with consideration of discontinuing pegvisomant if liver function tests are greater than 3-fold normal. In one study, the presence of Gilbert syndrome with a UGT1A1*28 genotype was predictive of increased hepatotoxicity caused by pegvisomant (165), although another study did not support this finding (166).

Evidence

Dopamine agonist. A meta-analysis showed that approximately 30% of patients attained biochemical control with cabergoline (167). Cabergoline is most likely to be useful in patients with just modest elevations of GH and IGF-1 levels, with or without concomitant hyperprolactinemia (168). Despite initial efficacy of cabergoline, the response to cabergoline appears to decrease with time. In one study, only 21% of subjects were controlled after 18 months of cabergoline administration (169). Therefore, cabergoline is felt to have more limited efficacy. Side effects include gastrointestinal upset, nasal congestion, fatigue, orthostasis, and headache. Cardiac valve abnormalities occur with high doses of cabergoline used for patients with Parkinson's disease but have not been observed in most studies of patients with prolactinomas treated with conventional doses (≤2.0 mg/wk) (170). One study in 42 acromegalic patients treated with cabergoline for a median of 35 months showed no increased risk of progressive valvular abnormalities (171).

Values and preferences

There is no clear consensus on frequency of cardiac valve monitoring with a patient on cabergoline. To monitor for cardiac valvulopathy, it may be reasonable to perform a baseline echocardiogram and then in serial fashion if doses > 2 mg/wk are used, but no clear recommendation is possible based on available literature.

Combination therapy

Combining medical therapies may improve efficacy, reduce side effects associated with an individual medication, decrease the frequency of injections and total drug dose, and, potentially offer a cost benefit and improved compliance during long-term treatment (172).

5.7 We suggest addition of pegvisomant or cabergoline in a patient with inadequate response to an SRL. (2|⊕⊕◯◯)

Evidence

SRL + pegvisomant. In studies of patients partially controlled (incomplete GH/IGF-1 normalization) despite high-dose SRL, the addition of pegvisomant (157, 173, 174) at a median dose of 60 mg weekly (range, 20–200 mg weekly, provided as a once- or twice-weekly injection) normalized IGF-1 in 95% of patients (172). Quality of life (175) and tumor size control (172) may be enhanced. However, there is an increased risk of transient transaminase elevation, reported in 27% of subjects, with the combination of SRL and pegvisomant (172).

SRL + cabergoline. Combined cabergoline- and SRL-normalized IGF-1 levels occurred in 42–60% of patients, and GH levels < 2.5 μg/L were achieved in 21–71% of patients whose levels had not normalized with a SRL alone (167, 175). This suggests that cabergoline may be added to a SRL, particularly if the GH/IGF-1 levels are mildly elevated.

Pegvisomant + cabergoline. In a prospective trial of 24 patients with acromegaly, cabergoline at 0.5 mg daily normalized IGF-1 in 11%, whereas addition of pegvisomant (10 mg daily) normalized IGF-1 in 68%, and subsequent discontinuation of cabergoline decreased the controlled percentage to 26% (176). In a retrospective study, 14 acromegalic patients uncontrolled with SRLs were switched to pegvisomant, 10–30 mg/d, but had persistent IGF-1 elevation. Addition of cabergoline at a final dose of 1.5 ± 0.7 mg/wk decreased IGF-1 by 18 ± 27.2%, producing a normal IGF-1 in 28% of patients (177). This suggests that the combination of pegvisomant and cabergoline might be useful in some patients.

5.8 We suggest use of an SRL as primary therapy in a patient who cannot be cured by surgery, has extensive cavernous sinus invasion, does not have chiasmal compression, or is a poor surgical candidate. (2|⊕⊕⊕◯)

Evidence

In a patient with a macroadenoma and associated extrasellar extension but no compressive mass effects, adjunctive therapy is frequently necessary after surgery because complete resection is not feasible. Administration of SRLs to patients as primary therapy has been associated with biochemical control in up to 70% of subjects, although subsequent studies indicate lower biochemical efficacy (146). Fifty percent tumor shrinkage has been found in approximately 59% of subjects after SRL administration and correlates with biochemical response (178). Therefore, primary medical therapy with an SRL may be useful in a patient whose tumor is primary extrasellar, eg, cavernous sinus, and cannot be removed surgically.

Values and preference

We recommend primary medical therapy for patients too ill for surgery or unwilling to undergo surgery. Financial considerations may determine the appropriate patient and physician therapeutic choice.

6.0 Radiotherapy (RT)/Stereotactic Radiotherapy (SRT)

6.1 We suggest use of radiation therapy in the setting of residual tumor mass following surgery, and if medical therapy is unavailable, unsuccessful, or not tolerated. (2|⊕⊕◯◯)

6.2 We suggest use of SRT over conventional radiation therapy in patients with acromegaly, unless the technique is not available, there is significant residual tumor burden, or the tumor is too close to the optic chiasm resulting in an exposure of more than 8 Gy. (2|⊕⊕◯◯)

6.3 To monitor the efficacy of radiation therapy, we recommend annual GH/IGF-1 reassessment following medication withdrawal. (1|⊕⊕⊕◯)

Evidence

RT is generally considered as an adjuvant therapy in a patient who is uncontrolled after surgery and medical therapy, and not as primary therapy (3, 5, 179). RT may even be considered in the setting of an aggressive tumor, including the presence of high Ki-67 staining, although there are no studies that address this (179). An advantage of radiation therapy is that it may lead to biochemical control, thereby limiting the necessity of lifelong medical therapy (5, 180). However, the full therapeutic effect may take many years, and a subset of patients may have limited response (181, 182). Therefore, medical therapy is required while awaiting the response to radiation therapy. After RT, we recommend periodic withdrawal of medical therapy for 1 to 3 months (depending on the specific drug) for reassessment of GH and IGF-1 levels.

In patients followed up to 15 years, remission rates of 10–60% have been reported with SRT (183–186). SRT includes a number of modalities, ie, gamma knife, CyberKnife, and a linear accelerator, which all deliver high-energy photons. A proton beam, which utilizes proton particles, is also used as SRT. SRT can therefore be delivered as a single dose (as with a gamma knife) or as a small number of fractions. In considering the use of SRT, it is critical to determine tumor distance from the optic apparatus because it is important to limit optic chiasmal exposure to less than 8 Gy in order to reduce chiasmal damage (187). Although the overall efficacy of SRT may be similar to conventional RT, time to remission may be shorter with SRT (186). In addition, SRT may be more appealing than conventional RT to patients because the treatment duration is shorter.

6.4 We recommend annual hormonal testing of patients following RT for hypopituitarism and other delayed radiation effects. (1|⊕⊕⊕⊕)

Evidence

Hypopituitarism occurs in more than 50% of patients within 5–10 years, and the prevalence increases with time (182, 188–190). The prevalence of hypopituitarism with

SRT appears similar to that after conventional RT (190–192). The risk of cerebrovascular disease in patients with acromegaly is increased after conventional RT (44). Complications of conventional RT in patients with pituitary tumors include radiation-induced cranial nerve damage, secondary tumors, radionecrosis, and cognitive changes (193–197). Radionecrosis is a rare complication of gamma knife SRT (198). It has been suggested that SRLs may limit the effectiveness of RT, although this finding was based on nonrandomized and retrospective studies and has been refuted by subsequent studies (183, 199, 200). Accordingly, there is no basis for the practice of withholding SRLs at the time of RT.

7.0 Special circumstances

Gigantism

7.1 In patients with the rare presentation of gigantism, we recommend the standard approaches to normalizing GH and IGF-1 hypersecretion as described elsewhere in this guideline. (1|⊕⊕⊕◯)

Evidence

Gigantism is caused by very rarely encountered sporadic or familial GH-secreting adenomas arising during childhood or puberty (201). GH hypersecretion occurring before epiphyseal closure results in excessive linear growth and phenotypic features of gigantism due to both elevated GH and IGF-1 levels (201). These deleterious effects of excess GH and IGF-1 on skeletal tissue are largely irreversible. Management of these patients should be rigorously tailored to achieve rapid and sustained attenuation of hormone hypersecretion as well as resection, ablation, or control of the pituitary tumor mass.

Because gigantism is extremely rare, evidence-based treatment recommendations are only sustained by very small uncontrolled single or series reports. These tumors are invariably large, usually invasive, and often associated with plurihormonal (especially prolactin) hypersecretion. Accordingly, management approaches including treatment combinations of more than one surgical procedure, combined medical treatments, and RT may all be required. Surgery is the first line of therapy, although adjuvant therapy is often required. Medical therapy with octreotide LAR has been successful (202), as has been the use of pegvisomant in subjects resistant to SRLs to control somatic complications and growth velocity (203–205).

Pregnancy

7.2 We suggest discontinuing long-acting SRL formulations and pegvisomant approximately 2 months before attempts to conceive, with use of short-acting octreotide as necessary until conception. (2|⊕⊕◯◯)

7.3 During pregnancy, we recommend that acromegaly medical therapy be withheld and administered only for tumor and headache control. (1|⊕⊕◯◯)

7.4 During pregnancy, we suggest serial visual field testing in patients with macroadenomas. (2|⊕⊕⊕◯)

7.5 We suggest against monitoring GH and/or IGF-1 levels during pregnancy. (2|⊕⊕⊕◯)

Evidence

In patients with acromegaly who have autonomous GH secretion and become pregnant, both the normal pituitary and placental variant forms of GH persist in the blood (206), and conventional assays usually cannot distinguish between these forms (207). The GH variant is biologically active, stimulates the production of IGF-1, and may raise IGF-1 levels above the age-adjusted normal range (207, 208). Therefore, there is limited use for monitoring either serum GH or IGF-1 in pregnant patients.

For the patient with acromegaly who becomes pregnant, there is a concern for a possible stimulatory effect of the pregnancy on somatotroph tumor size, the effects of GH excess on the mother, and the safety of medications used to treat acromegaly (209). In four patients, tumor growth and hemorrhage have been described during pregnancy, including a patient with progressive visual field loss (146, 210–213). Therefore, patients with acromegaly with macroadenomas should be monitored clinically for headaches and visual symptoms.

Because of GH-induced insulin resistance, the risk of gestational diabetes is modestly increased in acromegalic patients (214). The risk of gestational hypertension is also modestly increased (214). Cardiac disease has not proved to be problematic in pregnant women with acromegaly (209, 213–215).

Medical therapy should be considered in the setting of worsening headaches and/or evidence of tumor growth (216). In reports of almost 800 patients with prolactinomas, cabergoline has been shown to be safe for the developing fetus (217); this lessens concern for its use in patients with acromegaly. Fewer than 50 pregnant patients treated with SRLs at the time of conception have been reported; no malformations have been found in their children (209, 214, 215, 218). However, a decrease in uterine artery blood flow has been reported with short-acting octreotide (218), and one fetus appeared to have intrauterine growth retardation that responded to a lower dose of octreotide LAR (214). Octreotide binds to somatostatin receptors in the placenta (218) and crosses the placenta (218) and therefore can affect developing fetal tissues where somatostatin receptors are widespread, especially in the brain. Because of the limited data documenting safety, we recommend that long-acting depot formulations of SRLs be

discontinued if pregnancy is considered and that contraception be used when these drugs are administered. Short-acting octreotide sc injections can be utilized for disease control while awaiting conception. Considering the prolonged nature of the course of most patients with acromegaly, interruption of medical therapy for 9–12 months should not have a particularly adverse effect on the long-term outcome. On the other hand, these drugs can control tumor growth, and for enlarging tumors, their reintroduction during pregnancy may be warranted vs operating. Pegvisomant, a GH receptor antagonist, has been given to two patients with acromegaly during pregnancy without harm (209, 219), but the safety of this is certainly not established, and we recommend against its use during pregnancy.

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