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Acromegaly

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Acromegaly is a disease of exaggerated somatic growth and distorted proportion arising from hypersecretion of growth hormone (GH) and insulin-like growth factor 1 (IGF-1). The condition was described more than 120 years ago [1] and later ascribed to pituitary secretion and adenomas [2,3]. Acromegaly is a rare condition with a prevalence less than or equal to 70 cases per million and annual incidence of 3 to 4 cases per million [4,5]. The condition in children where there is accelerated growth of epiphyseal plates is referred to as gigantism rather than acromegaly.

Pathogenesis

Hypersecretion of GH or GH-releasing hormone (GHRH) can lead to acromegaly. Pituitary GH-secreting adenomas are responsible for 98% of acromegaly and almost exclusively are benign. The tumors usually are comprised of cells with sparsely or densely granulated cytoplasm secreting GH alone or a mixture of cells secreting either GH or prolactin (PRL). Less commonly, the tumor is composed of mammosomatotroph cells or the more aggressive acidophilic stem cell adenoma secreting GH and PRL. Plurihormonal adenomas secreting GH and many other hormones (PRL, thyrotropin, corticotropin, gonadotropins [follicle-stimulating hormone (FSH) and luteinizing hormone (LH)], and α subunit) are rare. Metastatic pituitary carcinoma secreting GH is extremely rare. Some clinically silent somatotroph adenomas are described as associated with high GH and IGF-1 levels [6].

Familial syndromes associated with GH hypersecretion include multiple endocrine neoplasia type 1 (germ cell inactivation of the *MENIN* tumor suppressor gene, which includes pituitary, parathyroid, and pancreatic tumors) [7,8], McCune-Albright syndrome ($G_s\alpha$ mutation; clinical appearance includes polyostotic fibrous dysplasia, cutaneous pigmentation, and pituitary hypersecretion) [9], and Carney complex (*PRKAR1A* gene mutations; clinical appearance includes skin pigmentation, mucocutaneous mixomatosis, cardiac myxoma, thyroid and breast lesions, and GH-secreting pituitary adenoma) [10]. Isolated familial acromegaly is described with loss of heterozygosity in chromosome 11q13 [11] and, recently, low-penetrance germline mutations in the aryl hydrocarbon receptor–interacting protein gene were found in individuals who had familial pituitary adenoma predisposition [12,13].

Other rare causes of GH hypersecretion are extrapituitary pancreatic islet cell tumors [14] and central (hypothalamic hamartoma, choristoma, and ganglioneuroma) [15] or peripheral (neuroendocrine tumors) GHRH oversecretion [16-18].

Exogenous administration of GH to non-GH deficient subjects as an athletic performance enhancer [19] or anti-aging treatment [20] has been a growing phenomenon during the last

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decade, exposing GH recipients to pathologies similar to those of patients who have endogenous GH hypersecretion.

Diagnosis

Signs and symptoms

Insidious clinical manifestation of GH excess resulting from a GH-secreting pituitary adenoma renders acromegaly a disease with typically delayed diagnosis, approximately 10 years from symptoms onset [21]. Changes in appearance bring only 13% of patients who have acromegaly to seek medical care [22], even though these changes account for 98% of presenting features [23].

Changes in appearance derive from skeletal growth, and soft tissue enlargement is subtle early in the course of the disease. Facial changes include large lips and nose, frontal skull bossing and cranial ridges, mandibular overgrowth with prognathism, maxillary widening with teeth separation, jaw malocclusion, and overbite. Increased shoe and ring size often are reported [22].

Large joint arthropathy is a common feature of the disease, occurring in approximately 70% of patients [24], resulting from cartilaginous and periarticular fibrous tissue thickening, causing joint swelling, pain, and hypomobility followed by narrowing of joint spaces, osteophytosis, and features of osteoarthritis with chronic disease [25]. Axial involvement is present in up to 60% of patients at presentation and includes disk space widening, vertebral enlargement, and osteophyte formation. Kyphoscoliosis occurs in 21%, cervical or lumbar linearization in 37%, and diffuse idiopathic skeletal hyperostosis in 20% of patients who have active acromegaly [26].

Skin thickening that is noticed mainly in the face, hands, and feet is the result of accumulation of glycosaminoglycans. Oversecretion and hypertrophy of sebaceous and sweat glands result in oily and sweaty skin, respectively. Pigmented skin tags and hypertrichosis are common features of the disease [27].

Upper airways obstruction is the consequence of macroglossia, prognathism, thick lips, and laryngeal mucosal and cartilage hypertrophy; it can cause sleep apnea and excessive snoring and can complicate tracheal intubation during anesthesia. Hypoventilation and hypoxemia also can arise from central respiratory depression [28] and kyphoscoliosis. Lungs show increased distensibility with normal diffusion capacity, suggesting an increase in alveolar size [29] or number [30].

The most common cardiovascular manifestation of acromegaly is biventricular cardiac hypertrophy that develops independently of hypertension and manifests early during the disease course. Approximately 90% of autopsied older patients who have longstanding acromegaly [31] and approximately 20% of young patients who have short disease duration [32] have biventricular cardiac hypertrophy. Diastolic dysfunction at rest or systolic dysfunction on effort can ensue and are exacerbated by exercise. If acromegaly is uncontrolled, diastolic heart failure follows exacerbated by the coexistence of hypertension, diabetes, and aging. The frequency of overt congestive heart failure in patients presenting with acromegaly ranges from less than 1% [33] to 10% [34]. Using highly sensitive angiography, postexercise ejection fraction increase was insufficient in 73% of patients who had active acromegaly [35] and in 40% of patients under age 40 [36]. Cardiac dysrhythmias [37-39] and late potentials [40] are more frequent and exacerbated by exercise. Arterial blood pressure (systolic and diastolic) is higher with loss of normal daily circadian variability [41]. Hypertension was reported in approximately one third of patients who had acromegaly [42,43]; however, whether

or not hypertension is more common than in the general population as yet is unclear. When the risk for coronary atherosclerosis was calculated based on clinical risk assessment and measurements of coronary arterial calcifications [44], 41% of patients were at intermediate to high risk for coronary atherosclerosis.

Peripheral paresthesias, symmetric peripheral sensory and motor neuropathy, proximal myopathy, myalgia, and cramps are encountered. Carpal tunnel syndrome develops with medial nerve compression resulting from wrist synovial edema and ligament and tendon growth [45]. Exophthalmos [46] and open-angle glaucoma [47] may develop with hypertrophy of extraoccular tissue and around Schlemm's canal.

Hyperprolactinemia with or without galactorrhea develops in approximately 30% of patients [48] because of pituitary stalk compression or mixed tumor secretion of GH and PRL. Hypopituitarism ensues by mass compression of normal pituitary tissue in approximately 40% [49] of patients; amenorrhea or impotence [50] or secondary thyroid [51] or adrenal failure can develop. Goiter and thyroid abnormalities are common [52,53], potentially as a result of IGF-1–stimulating effects on thyrocyte growth. Hyperthyroidism rarely develops because of high levels of serum thyrotropin secreted from plurihormonal pituitary tumors [53]. Rarely, Cushing's disease develops when the pituitary tumor cosecretes GH and corticotropin [54] or as part of the McCune-Albright syndrome [55].

Insulin resistance and diabetes mellitus occur as a result of direct anti-insulin effects of GH [56,57]. GH stimulation of 1α-hydroxylase activity increases levels of serum 1,25-dihydroxycholecalciferol, resulting in intestinal calcium absorption and hypercalciuria [58]. Osteoporosis may occur as a consequence of secondary gonadal failure [59,60]. A recent cross-sectional study showed that postmenopausal women who had acromegaly develop vertebral fractures in relation to disease activity (IGF-1 and duration). Moreover, vertebral fractures occur even in the presence of normal bone mass density [61].

A direct cause-effect association between acromegaly and cancer initiation has not been proved [62,63] and the controversy as to whether or not the risk for developing cancer in patients who have acromegaly differs from that of the general population is ongoing [64]. Cancer incidence in patients who had acromegaly was not increased in a critical analysis of nine retrospective reports (1956–1998; 21,470 person-years at risk) [63]. Benign colon polyps (adenomatous and hyperplastic) have been reported in 45% of 678 acromegalic patients in 12 prospective studies [63]; however, this incidence seen in patients who had acromegaly is similar to that of the general population [65]. The prevalence of recurrent colon adenomas (but not hyperplastic polyps) correlated with serum IGF-1 levels [66]. Three or more skin tags is a reliable screen for colon polyps in patients over age 50 who have 10 or more years of active disease [67]. In a large literature review, colon cancer was reported in 2.5% of 678 patients who had acromegaly [63]. In 1362 patients who had acromegaly in the United Kingdom, colon cancer mortality but not incidence was higher than in the general population and correlated with GH serum levels [68]. Patients who had active acromegaly should be screened by colonoscopy at baseline and than every 3 to 5 years depending on coexisting risks factors [69].

Mortality ratio in acromegaly calculated from retrospective analysis over the past 30 years is increased significantly compared with healthy subjects [70-73]. Age- and gender-adjusted standardized mortality ratio (SMR) in patients from Finland who had acromegaly and basal serum GH concentration greater than 2.5 μg/L approximately 5 years from beginning of treatment was 1.63 (CI, 1.1–2.35; $P<.001$) with post-treatment IGF-1 plasma levels not affecting mortality [72]. In a study from New Zealand, observed to expected mortality ratios were 2.6 (95% CI, 1.9–3.6), 2.5 (1.6–3.8), 1.6 (0.9–3), and 1.1 (0.5–2.1) for patients who had 5 or more, less than 5, less than 2, and less than 1 μg/L last follow-up baseline serum GH levels,

respectively (*P*<.001). Also serum IGF-1 levels (SD score) correlated with mortality ratios. Independent predictors of survival by multivariate analysis were last serum GH level (*P*<.001), last IGF-1 SD score (*P*<.02), age, duration of symptoms before diagnosis (*P*<.03), and hypertension (*P*<.04) [71]. In the West Midlands pituitary database, age-and gender-adjusted SMR of 1.26 (CI, 1.03–1.54; *P*<.046) was calculated for patients who had acromegaly. Post-treatment basal GH levels greater than or equal to 2 μg/L increased ratio of mortality rates to 1.55 (CI, 0.97–2.50; *P*<.068) and radiotherapy to 1.67 (CI, 1.09–2.56; *P*<.018). In this study, IGF-1 was not a predicting factor. Leading causes of death were cerebrovascular and cardiovascular and respiratory disease [70]. Whether or not GH, IGF-1, or both can be independent predictors of mortality requires further assessment as the assays used to measure them increase in sensitivity and specificity.

Biochemical markers

Considering the limitations of GH and IGF-1 biochemical assays currently available and the nonstandardized reporting of results gathered in different studies [74-76], the cutoff defining acromegaly from normalcy is unclear. From an international consensus point of view, however, absolute numbers are used when discussing disease control rather than cure.

Nadir GH serum levels should be below 1 μg/L, preferably less than 0.4μg/L, in the 2 hours after 75-g oral glucose load (oral glucose tolerance test [OGTT]) [69,77]. This criterion often is used for diagnosis of acromegaly and for follow-up during treatment. Serum GH concentrations are affected by circadian periodicity, pulsatile secretion, exercise, starvation, and blood glucose levels. This cutoff is based on the sensitivity of recent sandwich-type immunometric assays with a sensitivity of 0.2 μg/L and even 0.001 μg/L. These assays have replaced competitive radioimmunoassays with detection sensitivity of 0.3 to 0.5 μg/L. Trials conducted for assays' external quality assessment schemes show lack of standardization and method dependent variability, in many cases of up to 100%. Assay imperfections are the result of a variety of factors, including the use of monoclonal versus polyclonal antibody, sensitivity of the antibody to different GH isoforms (that also may change between patients), the inability to apply a linear "conversion factor," the use of more than one standardization international reference GH preparation (currently preferred is the 22-kd GH International Reference Preparation (IRP) 98/574) [78], and whether or not plasma GH-binding proteins interfere in the antibody and specific epitope interaction. Efforts currently are underway to overcome these challenges. For now, these confounding factors should be taken into consideration with regard to agreement on a cutoff value to determine disease activity, especially with borderline GH values [75,79]. GH measurements after an OGTT are unreliable in patients who have uncontrolled diabetes mellitus or liver or renal diseases, in patients receiving estrogens, or in patients who are pregnant and during late adolescence [69].

Age and gender serum IGF-1 levels should be within normal ranges. The long half-life and stable (as compared with GH) serum levels of IGF-1 allow for assessment of disease activity. Several factors affect serum IGF-1 levels and need to be taken into account for interpretation. IGF-1 is affected dramatically by age; however, a uniform standard for optimal age ranges has not been established; moreover, body mass index and racial differences currently are not accounted for in most assays. Methods used for removal of IGF binding proteins that interfere with sensitivity and reproducibility differ in their effciency; IGF-1 standard references differ between laboratories as do the affinity and specificity of the antibodies used. Other physiologic factors that influence IGF-1 concentrations include circadian rhythm, nutrition, insulin, thyroxine, and steroid levels [76].

Ideally, GH and IGF-1 values should be obtained to complement evidence for assessing disease activity; however, a discrepancy between abnormal GH levels coexisting with normal IGF-1 serum levels is not encountered uncommonly [80].

Imaging

Pituitary MRI with contrast material is most sensitive for determining a pituitary source of GH oversecretion, detecting tumors as small as 2 mm. MRI also can visualize tumor dimensions, invasiveness, and proximity to the optic chiasm. When the GH source is extrapituitary, CT, MRI, or both can be used to localize the ectopic source [77].

Treatment

Treatment should aim at managing the tumor mass and GH hypersecretion to prevent morbidity and increased mortality while preserving normal pituitary function (Table 1).

Surgery currently is the preferred approach for treating most patients. Serum GH levels are controlled within an hour after complete removal of the GH-secreting adenoma. Transsphenoidal microsurgical adenomectomy approach is used most commonly and, in the hands of experienced neurosurgeons, cures the majority of patients who are harboring a well-circumscribed microadenoma and who have serum GH levels less than 40 μg/L [81-83]. In general, approximately 80% of patients who have microadenoma and approximately 50% of those who have macroadenoma normalize serum IGF-1 levels after transsphenoidal adenomectomy [84,85]. In a recent retrospective study of 506 patients in one center, during 19 years, who underwent transsphenoidal surgery, cure rates (as defined by basal GH serum levels less than or equal to 2.5 μg/L, post-OGTT GH serum levels less than or equal to 1 μg/L, and normal IGF-1) were 75% for microadenomas and 50% for macroadenomas. These tests used different biomarker assays, affecting biochemical remission definition and, therefore, the reported percentage of patients in remission. Remission rate in patients who have intrasellar macroadenomas, suprasellar macroadenomas without visual field impairment or visual field impairment, tumors with parasellar or sphenoidal expansion, or giant adenomas were 74%, 45%, 33%, 42%, and 1%, respectively [86]. Transsphenoidal surgery was required for recurrent tumor in 0.4% of patients; however, approximately 6% is reported in a previous literature review [69] and usually is the result of incomplete resection. Presurgical hypopituitarism improved in 30% of patients after transsphenoidal adenomectomy, did not change in 50%, and worsened in 2% [86].

Post-transsphenoidal surgical mortality is rare and most side effects are transient. Permanent diabetes insipidus, cerebrospinal fluid leak, hemorrhage, and meningitis develop in up to 5% [69], and their frequency correlates with tumor size, invasiveness, and neurosurgical experience [81]. Other approaches include endoscopic transsphenoidal and transnasal pituitary surgery, which can be undertaken with intraoperative MRI. These approaches maximize the extent of tumor resection; however, whether or not they improve remission rates is yet to be assessed [87,88].

Somatostatin receptor ligands

Somatostatin receptor ligands (SRLs) are the first-choice pharmacotherapy for treating patients who have acromegaly. Two formulas are available for treatment of acromegaly octreotide (Novartis) and lanreotide (Ipsen). Short- and long-acting derivatives of these molecules have been developed. Both bind to somatostatin receptor subtype 2 (SST2) with high affinity and, to a lesser extent, SST5, whereas octreotide also exhibits some SST3 affinity [89]. For clinical use only, octreotide compounds are approved in the United States. Octreotide acetate (Sandostatin) is a cyclic octapeptide administered by deep subcutaneous or intravenous injections. The typical starting dose is 100 to 250 μg thrice daily up to 1500 μg daily [90,91]. Sandostatin LAR Depot is a long-acting octreotide compound. Octreotide acetate encapsulated within microspheres is administered as an intramuscular injection every 4 weeks. Starting dose is 20-mg monthly increasing up to 40 mg depending on clinical and biochemical responses.

Lanreotide (Somatulin SR) contains lanreotide (30 or 60 mg) incorporated into a biodegradable polymer microparticle, allowing prolonged release after intramuscular injection every 7 to 14 days. Somatulin Autogel is a depot preparation of lanreotide delivered as an aqueous, small-volume mixture (60, 90, or 120 mg) in prefilled syringes for deep subcutaneous administration every 28 days [92].

Most studies assessing SRLs efficacy in acromegaly define disease control by mean fasting random serum GH levels less than 2.5 μg/L or normalization of age- and gender-matched IGF-1 plasma levels [93]. Sandostatin LAR suppressed GH and IGF-1 levels in 65% and 63% of patients, respectively [70,93-106], whereas Somatulin SR (30 mg every 7 to 14 days) suppressed GH and IGF-1 levels in 55% and 54% of patients, respectively [100,102, 107-111]. Treatment with Somatulin SR (60 mg every 21 or 28 days) reduced GH less than 2.5 μg/L in 76% of patients [96,112]. Somatulin Autogel (up to 120 mg every 21 or 28 days) is not shown superior to the other lanreotide compounds [113-116]. If mean fasting baseline serum GH levels less than 1 μg/L are the cutoff for remission, 33% of patients treated with Sandostatin LAR [96,100,103,106] and 25% those treated with of Somatulin SR [96,100] are controlled. Biochemical control improves with longer treatment duration as IGF-1 plasma levels continue to decrease over the years [70,94-96,99,104,117,118]. Primary pharmacotherapy is used for selected patients [94,119]. Approximately 65% of patients receiving either primary or adjuvant SRLs treatment exhibit serum GH levels less than or equal to 2.5 μg/L (64%) or normalization of IGF-1 [70,94,96-99,107], even though treatment-naive patients exhibit higher pretreatment GH and IGF-1 levels than those treated previously with surgery or radiotherapy [96,99]. These studies also demonstrate tumor shrinkage with SRL treatment. Seventy percent tumor shrinkage was demonstrated with Sandostatin LAR, 26% with Somatulin SR (30 mg), and 39% with Somatulin SR (60 mg), and data are not yet reported for Somatulin Autogel [93]. With primary SRLs pharmacotherapy, 79% tumor shrinkage was evident with Sandostatin LAR [94,96,99], 50% with Somatulin (60 mg) [96], and 25% with Somatulin (30 mg) [107,109].

Sandostatin LAR [96,109,120] and Somatulin SR [120-122] reduced left ventricular hypertrophy, improved diastolic dysfunction, improved sleep apnea [70], and improved lipid profile [96,123,124]. Improvement in headache, perspiration, paresthesias, fatigue, osteoarthralgia, and carpal tunnel syndrome and reduction in soft tissue enlargement are reported [94,99,103,106,114,116].

Side effects are documented extensively for Sandostatin LAR, according to manufacturer reports [95,96,99,103-106,125,126], Somatulin Autogel [95,113,114,116] and Somatulin SR [96,100,108,110,111,115,127-130] usually are mild to moderate in severity and transient. Most common side effects include gastrointestinal symptoms, such as abdominal discomfort, flatulence, diarrhea or constipation, and nausea. Biliary tract abnormalities, including gallstones, microlithiasis, sediment, sludge, and dilatation, are reported in up to 50% of patients and develop during the first 2 years of treatment and tend not to progress thereafter. Asymptomatic cholelithiasis is described in 20% to 40% of patients and approximately 1% of these patients require cholecystectomy. Injection site irritation and pain usually is mild and dose dependent. Asymptomatic sinus bradycardia is described in up to 25% and conduction abnormalities in up to 10% of patients treated with subcutaneous octreotide acetate. Abnormal glucose metabolism is described with the use of SRLs, as activation of SST2 and SST5 in the pancreatic insulin-secreting beta cells likely inhibits insulin secretion and counter-regulatory hormones, such as glucagon. Mild hyperglycemia and, rarely, hypoglycemia [131], manifest mostly in patients who have pre-existing glucose abnormalities. Octreotide alters nutrient absorption and may alter gastrointestinal drug absorption. Blood levels of cyclosporine may be attenuated, resulting in transplant rejection. Altered absorption of oral hypoglycemic agents, b-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance may

ensue; hence, patient monitoring is required and dose adjustments of these therapeutic agents is recommended. Somatostatin might decrease cytochrome P450 enzyme action; therefore, drugs metabolized mainly by CYP3A4 and that have a low therapeutic index (eg, quinidine, terfenadine, and warfarin) should be used cautiously [126]. SRLs should be avoided in patients treated with drugs known to commonly prolong QT interval, such as cisapride [123].

Growth hormone receptor antagonist

Pegvisomant (Somavert, Pfizer) is a pegylated GH receptor (GHR) antagonist approved for treatment of acromegaly that interferes with the signaling of the GH receptor, inhibiting subsequent IGF-1 generation. Pegvisomant binds through a high affinity site 1 to one GHR dimer subunit but cannot bind through a mutated site 2 to the second GHR dimer subunit, resulting in failure to initiate subsequent GH signal transduction pathways [132-136]. Pegvisomant is more potent than SRLs for inhibition of peripheral IGF-1 levels. Daily pegvisomant (20 mg) given for 12 weeks, normalized IGF-1 levels in 82% of patients who had acromegaly [137]. Daily doses (up to 40 mg given for 12 months) normalized IGF-1 levels in 97% of patients [138]. Open-label, prospective, 1-year treatment with pegvisomant (10–40 mg) in 12 patients resistant to high-dose SRLs reduced IGF-1 serum levels in all patients, with normalization achieved in 75%. In another multicenter, open-label, 32-week trial, 53 patients who had acromegaly, treated previously with octreotide LAR, were switched to pegvisomant (10–40 mg, adjusted based on serum IGF-1 concentrations). At the end of the study, IGF-1 levels were normalized in 78% of patients [139].

Dose-dependent regression of soft tissue swelling, excessive perspiration, and fatigue were observed [137]. Pegvisomant also improves insulin sensitivity and glucose tolerance, reducing fasting serum insulin and glucose levels [138-142]. Glycated hemoglobin (HgA1C) was not decreased in patients treated for 12 [140,142] or 18 months [138]; however, in a multicenter, open-label trial, 53 patients who had acromegaly who were switched from octreotide LAR to pegvisomant reported decreased HgA1C levels after 32 weeks' treatment [139]. Serum GH levels are increased as much as 76% over baseline levels and persistent tumor growth is reported [138], even though, in most cases, GH-secreting adenoma volumes do not change [138-140, 143]. Current recommendations are to perform a pituitary MRI every 6 months in all patients [69]. Elevation of serum transaminases are reported, which, at times, may necessitate drug discontinuation [138,140,144]. Idiosyncratic chronic active hepatitis, with elevated transaminases more than 3 times above the upper normal range, was reported in 9% of patients receiving pegvisomant for more than a year. Liver biopsy in a single patient revealed chronic mild hepatitis with mixed portal inflammation, including eosinophilic granulocytes [145]. Current recommendations are to assess liver function tests before and monthly during the first 6 months' treatment and, thereafter, every 6 months [69].

Pegvisomant should be considered in patients resistant to SRLs and also can be administered in combination with octreotide. This offers improved serum IGF-1 levels and improved control of altered glucose metabolism and permits the use of lower doses of a costly drug [146,147]. Because serum GH levels are elevated during pegvisomant treatment, serum IGF-1 levels are the only marker to be used for follow-up. Recurrent pegvisomant injections in one area of the abdominal wall produced lipohypertrophy at injection sites. Therefore, the drug is recommended for injection in different body areas [148]. Possible overtreatment with pegvisomant causes GHR resistance-GH deficiency similar to features of adult GH deficiency and doses of pegvisomant should be monitored carefully during treatment to avoid IGF-1 deficiency.

Dopamine analogs

Bromocriptine and carbegoline have been used as adjuvant therapy for acromegaly [149]. Bromocriptine suppresses serum GH level to less than 5 μg/L in less than 15% of patients who have acromegaly when used in high doses (up to 20 mg per day), and patients report reduced soft tissue swelling, perspiration, fatigue, and headache. Carbegoline is a long-acting dopamine agonist that reduced serum GH levels to less than 2 μg/L and normalized IGF-1 in approximately 30% of patients [150,151]. Side effects include gastrointestinal discomfort, transient nausea and vomiting, nasal congestion, dizziness, postural hypotension, headache, and mood disorders [150]. In light of recent studies demonstrating increased incidence of valvular heart disease with high doses of carbegoline [131,152], this mode of treatment should be undertaken with caution.

Radiotherapy

Radiotherapy usually is reserved for patients who have postoperative persistent or recurrent tumors that are resistant or intolerant to medical treatment. Conventional external deep X-ray therapy usually is given over 5 to 7 weeks in 1.8-cGy doses to a maximum accumulating dose of 40 to 50 cGy. In a multicenter retrospective study encompassing 884 irradiated patients, investigators report a gradual decrease in basal serum GH levels over 20 years correlating with preirradiation basal serum GH levels. Basal GH serum levels were less than 2.5 μg/L in 22% of patients after 2 years, 60% by 10 years, and 77% by 20 years [153]. IGF-1 levels were attenuated in parallel to GH levels in 63% of patients achieving normal ranges after 10 years. Ten years after irradiation, 27% of patients developed thyrotropin deficiency, 18% FSH/LH deficiency, and 15% corticotropin deficiency. Secondary intracranial tumor formation or visual impairment was not observed [153]. Similar results were observed previously, showing that conventional megavoltage irradiation of GH-secreting tumors prevented tumor growth in 99% of patients with a predictable fall in GH serum levels reaching 90% 15 years post irradiation, without evidence of side effects other than pituitary axes deficiencies [154].

Stereotactic radiosurgery using gamma knife delivers a single tumor-focused radiation fraction. A recent study retrospectively analyzed 96 patients who had acromegaly 12 to 120 months after gamma knife radiosurgery (mean follow-up 53 months). Serum IGF-1 levels normalized within 54 months and post-OGTT serum GH levels were less than 1 μg/L after 66 months in 50% of patients. Adenoma growth arrest was observed in all, and shrinkage occurred in 62% of patients. Hypopituitarism developed in 26% of patients only when irradiated by 15 Gy or more [155]. Gamma knife radiosurgery requires precise delineation of the tumor target to allow exact focusing with minimal surrounding tissue exposure, especially to the optic tract.

Treatment approach

For patients who have newly diagnosed acromegaly and a microadenoma or a well-defined intrasellar adenoma, a surgical approach is preferred, as cure is highly probable in the hands of experienced neurosurgeons (Fig. 1). Because surgery may not be curative for patients who have macroadenomas, especially if invasive, other treatment approaches can be undertaken. Tumor debulking is necessary if there is evidence for pressure on the optic chiasm or other vital organs. There is insufficient scientific evidence to support tumor debulking in other instances; however, this approach is taken commonly and there is evidence for enhancement of SRLs action if 75% of the mass adenoma is resected [94,156]. Surgery also should be considered if patients are anticipated to be noncompliant. Primary pharmacotherapy should be considered in newly diagnosed patients who have invasive macroadenoma, especially if patients are reluctant to undertake surgery or cannot endure the procedure. Primary pharmacotherapy usually is a long-acting SRL. The GH receptor antagonist should be

considered in patients who have uncontrolled diabetes mellitus where SRLs may exacerbate glucose abnormalities or in patients resistant to or those who cannot tolerate SRLs treatment.

Patients who have persistent or recurrent GH-secreting pituitary adenoma usually are considered for pharmacotherapy, unless there are clear indications for second surgery. SRLs usually are the first choice, with pegvisomant as an alternative treatment or as an adjuvant with SRLs, providing a “sparing effect” on daily dose requirements. Increasing dosing frequency is more efficacious than increasing dosing per se. Radiotherapy usually is the last choice for adjuvant therapy when patients are resistant to other medications or cannot tolerate, cannot afford, or refuse long-term pharmacologic treatment. Pharmacotherapy, however, may be required for years after radiation for effective disease control.

Signs and symptoms of acromegaly and serum biomarkers should be monitored quarterly until biochemical control is achieved and the disease is inactive. Thereafter, regardless of the treatment used, annual clinical, biochemical, and MRI evaluations are suggested. Disease recurrence is unlikely if post-OGTT serum GH levels are less than 1 μg/L and IGF-1 is within the normal range. Subtle serum GH elevations can predict recurrence, however, even if serum IGF-1 levels are normal [80], and, conversely, increased serum IGF-1 levels indicate relapse even if serum GH levels are less than 1 μg/L [157]. Patients should be monitored for signs of local tumor growth, including deterioration in visual fields, increased headache, or other signs of mass effect, especially when treated with pegvisomant. Glucose abnormalities, liver function tests (with pegvisomant), endogenous pituitary reserve, cardiovascular function, pulmonary status, and rheumatologic complications should be assessed carefully. Mammography, colonoscopy, and prostate evaluation should be followed as for the general population. Gallbladder ultrasonogram should be performed for signs and symptoms indicating possible cholelithiasis or cholecystitis. Fertility and cosmetic treatments and psychologic support may be required. Patients should be taught about their disease, its complications, modes of therapy, and, if possible, to self-inject medications if so preferred.

Summary

Acromegaly is a rare disease caused by GH hypersecretion, mostly from a pituitary adenoma, driving IGF-1 overproduction. Manifestations include skeletal and soft tissue growth and deformities and cardiac, respiratory, neuromuscular, endocrine, and metabolic complications. Increased morbidity and mortality require early and tight disease control. Surgery is considered the treatment of choice for microadenomas and well-defined intrasellar macroadenomas. Complete resection of large and invasive macroadenomas rarely is achieved, however, hence their low rate of disease remission. Pharmacologic treatments, including long-acting somatostatin analogs, dopamine agonists, and GH receptor antagonists, have assumed more importance in achieving biochemical and symptomatic disease control.

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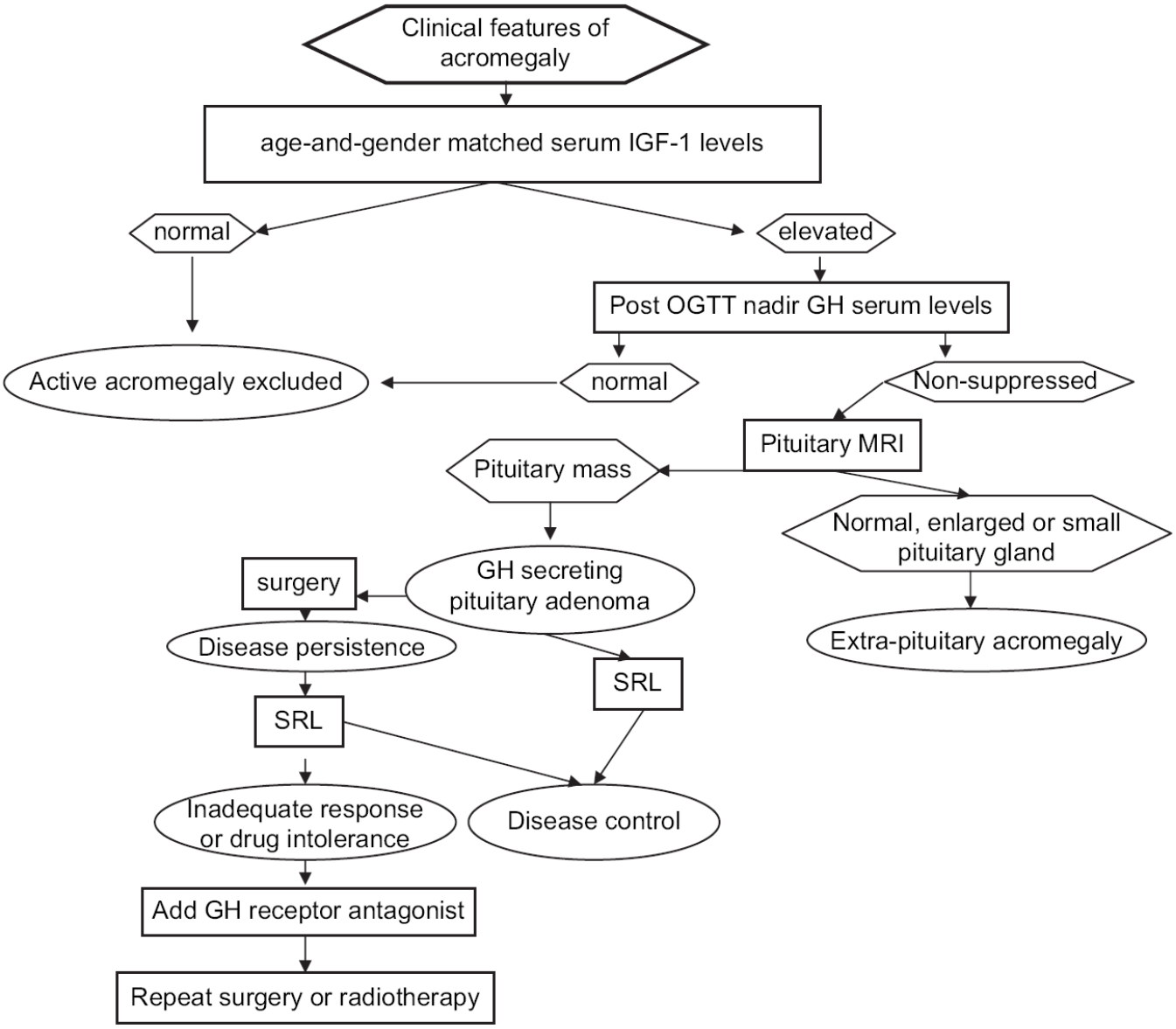

Fig. 1.

Treatment approach to a patient with acromegaly. (*Modified from* Melmed S. Medical progress: acromegaly. N Engl J Med 2006;355(24):2558–73; with permission. Copyright © 2006, Massachusetts Medical Society. All rights reserved.)

Table 1

Results of acromegaly treatment

	Surgery	Somatostatin receptor ligands	Growth hormone receptor antagonist	Dopamine agonist	Radiotherapy
Type of therapy or dose of drug	Transsphenoidal resection	Octreotide (50–400 μg every 8 hours) Octreotide LAR (10–40 mg IM every 4 weeks) Lanreotide SR (30 or 60 mg IM every 10 or 14 or 21 days) Lanreotide gel (60, 90, or 120 mg deep SC every 4 weeks)	Pegvisomant (10–40 mg SC daily)	Bromocriptine (up to 20 mg daily) Cabergoline (1–4 mg orally weekly)	Conventional or radiosurgery
Biochemical control					
Mean fasting serum GH level < 2.5 μg/L	Macroadenomas < 50% Microadenomas >80%	Approximately 65%	Increases	<15%	60% in 10 years
Serum IGF-1 level normalization	Macroadenomas < 50% Microadenomas >80%	Approximately 65%	O90%	<15%	60% in 10 years
Onset of response	Rapid	Rapid	Rapid	Slow (weeks)	Slow (years)
Patient compliance	One-time consent	Must be sustained	Must be sustained	Good	Good
Tumor mass	Debulked or resected	Growth constrained or shrinkage	Unknown	Unchanged	Ablated
Disadvantages					
Cost	One time charge	Ongoing	Ongoing	Ongoing	One-time charge
Hypopituitarism	10%	None	Very low IGF-1 if overtreated	None	>50%
Other	Tumor persistence or recurrence: 6%	Gallstones 20%	Elevated liver enzymes	Nausea 30%	Local nerve damage
	Diabetes insipidus: 3%	Nausea; diarrhea		Sinusitis	Visual and CNS disorders, 2% cerebrovascular risk
	Local complications: 5%			High dose required	

Goals of acromegaly management include controlling GH and IGF-1 secretion and tumor growth, relieving central compressive effects, preserving or restoring pituitary function, treating co-existing illnesses, preventing premature death, and preventing disease recurrence. Percentages denote an approximation of patients having the result after treatment.

Abbreviations: CNS, central nervous system; IM, intramuscular; LAR, long-acting release; SC, subcutaneous; SR, slow release.

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