ACROMEGALY: UNDERSTANDING A RARE MULTISYSTEM DISEASE

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ABSTRACT

Acromegaly is a rare disorder, resulting from a pituitary adenoma that overproduces a growth hormone (GH) and leads to excess growth of soft tissues and disruption in certain metabolic pathways. Because GH affects numerous systems, acromegaly manifests in numerous ways, which affect morbidity and mortality. The physical changes are disfiguring (enlarged nose, lips, hands, feet), uncomfortable (excessive sweating, headaches, dizziness, arthritis), and dangerous (hypertension, type 2 diabetes mellitus, cardiovascular disease). The onset of acromegaly is insidious and seemingly benign, so the signs and symptoms are often ignored or are associated with other more common causes. By the time a patient with acromegaly sees an endocrinologist for diagnosis and treatment, the signs and symptoms already have become distressing and, in some cases, permanent. However, once acromegaly is suspected, diagnosis is straightforward and can be performed by practitioners in other areas of medicine who come into frequent and regular contact with patients. There are several treatments available for acromegaly: surgery to remove or debulk the adenoma, pharmacotherapies that target different steps to control GH secretion or action, and radiation therapy.

No single therapy provides complete control of the disease in 100% of the cases, and each therapy has its own advantages and disadvantages. However, treatment success rates are high. The goal of this article is to review and describe the presentation of the treatment options for acromegaly, so that practitioners other than endocrinologists will consider acromegaly in the differential diagnosis of the more common signs and symptoms, thus diagnosing and treating the disorder earlier.

Acromegaly is a rare disorder of the pituitary resulting from its overproduction of growth hormone (GH). Because of the widespread effects of GH in the body, acromegaly manifests in many ways: most notably, the unusual and excess growth of soft tissues. If clinicians are to understand acromegaly, they must first understand the mechanisms regulating GH biosynthesis and secretion.

The pituitary, a small gland located at the base of the brain, produces several important hormones for growth and development, reproduction, and metabolism. GH, the most abundantly produced hormone from the anterior pituitary, is secreted by somatotrope cells, which account for 50% of the hormone-secreting cells in the anterior pituitary. Upon activation, somatotropes release GH into the bloodstream, and circulating GH induces production of an insulin-like growth factor (IGF)-1 by the liver and many other tissues. IGF-1 is the actual hormone responsible for bone...
and tissue growth (Figure 1). IGF-1 receptors are present in all tissues of the human body. This cascade of hormone release is controlled by the hypothalamus and by negative feedback. GH release, which is secreted by the hypothalamus, is reduced by somatostatin. Its production is controlled by circulating GH and IGF-1 levels. GH production and release is upregulated by another hypothalamic hormone, GH-releasing hormone (GHRH). In fact, the hypothalamus secretes 6 hormones that regulate the pituitary: GHRH, somatostatin, gonadotropin-releasing hormone, thyrotropin-releasing hormone, corticotropin-releasing hormone, and dopamine. As will be discussed later in this article, 2 of these hormones are now therapeutic targets for the treatment of acromegaly.

In healthy individuals, GH is normally secreted in discrete irregular bursts throughout a 24-hour period, with the most frequent secretion during the night. In between these bursts, blood levels of GH fall to undetectable levels. GH secretion also fluctuates throughout a person’s lifetime—high levels during childhood, peaks during adolescence, and lowest levels during aging. Several internal and external factors also modulate GH synthesis, such as neurotransmitters (ie, serotonin, dopamine, and alpha-adrenergic agonists), in addition to plasma glucose, exercise, stress, emotional excitement, and ingestion of protein-rich meals. GH has many peripheral effects. The metabolic effects of GH are opposite those of insulin: increased hepatic glucose output, decreased glucose utilization, and increased lipolysis, thus shifting the body’s energy source from carbohydrates to fats, and promoting a diabetic state. GH also leads to somatic growth and has a critical role in the development of normal skeletal muscle, myocardial muscle, and bone.

Etiology and Pathogenesis of Acromegaly

Overproduction of GH in acromegaly is the result of a benign, pituitary somatotropic adenoma in more than 90% of cases; carcinomas of the pituitary are exceedingly rare. Depending on the tumor size, pituitary adenomas are termed as microadenomas (≤1 cm) or macroadenomas (>1 cm). Their growth can be slow and insidious or rapid; in either case, signs of acromegaly usually do not manifest until a person is of middle age. In cases of prepubescent GH overproduction, excessive linear growth is the major outcome and is referred to as gigantism. In most cases, acromegaly is not a genetic disorder; the genetic mutation that signals tumor growth is acquired, not inherited. Rarely, acromegaly may be inherited as part of a MEN-1 (multiple endocrine neoplasia type 1) syndrome or as familial acromegaly.

Clinical Presentation

Symptoms of acromegaly are caused directly by overproduction of GH or the mass effect of the growing tumor. Classic symptoms caused by excess GH include outwardly obvious changes: enlarged facial features (ie, enlarged nose, lips, forehead [frontal bossing]), voice changes, increased spacing of teeth, gross widening of hands and feet, abnormal protrusion of the mandible (prognathia), enlarged tongue, oily skin or increased acne, profuse sweating, and galactorrhea. However, these manifestations have a slow and insidious onset and patients, in retrospect, may have the disease for at least 10 years before diagnosis. Other changes include menstrual disturbance, carpal tunnel syndrome caused by swollen tissue compressing the nerves, hypertension, type 2 diabetes mellitus, cardiomegaly, obstructive sleep apnea, thyromegaly, diffuse organomegaly, and overgrowth of bone and cartilage leading to arthritis.

Symptoms, including headache and compromised visual function (loss of peripheral vision and blurred vision), are caused by the actual mass of the tumor (as...
REVIEW

opposed to the hormones it secretes) and the close proximity of the pituitary to the optic chiasm, optic nerve, and cavernous sinuses. If the tumor grows large enough, there may be compression of the anterior pituitary, resulting in loss of hormonal function: first, disruption of the luteinizing hormones/follicle-stimulating hormone (gonadotropins), followed by the thyroid-stimulating hormone, and the adrenocorticotropic hormone. Amenorrhea, impotence, and decreased libido are caused by the tumor disrupting gonadotropin secretion and are common in acromegaly.

The challenge for any practitioner is recognizing the signs of acromegaly early to prevent the patient having permanent tissue changes and invasion by the tumor into other brain areas. Also, acromegaly is associated with several severe comorbidities that affect mortality rates, including type 2 diabetes mellitus, hypertension, cerebrovascular and cardiovascular disease, and possibly increased risk for colon cancer.2-4

The signs of acromegaly are common and often subtle physical changes, and the disorder is relatively rare. Therefore, the clinicians who diagnose acromegaly often are not endocrinologists but rather those clinicians in primary care settings or other medical settings that involve regular patient visits (e.g., internists/family medicine physicians, obstetricians/gynecologists, ophthalmologists, neurologists, dentists, and nurses). Family members and friends (especially those people who do not see the patient every day but perhaps only every few years) may be among the first to notice the patient’s acromegalic signs. These signs and symptoms often occur in clusters, thus helping to distinguish the disorder from other more common causes. Ultimately, a clinician should recognize symptom clustering and at least consider acromegaly during the differential diagnosis of a patient’s more benign presenting symptoms, such as headache, amenorrhea, excessive acne, dental changes, and ring and shoe size changes.

Clinical situations in which healthcare providers should consider acromegaly as a possible diagnosis include new-onset diabetes, unexplained new-onset headache, hypogonadism or impotence, menstrual irregularities, amenorrhea, unexplained arthritis, increase in ring size without weight gain, adult changes in dental anatomy, or heat intolerance. For dentists, the common first signs of acromegaly include the forward and downward growth of the mandible, enlarged mandible, increased dental spacing, and malocclusion. The opening of the bite usually prompts a consultation with a dentist. Other oral signs include an enlarged tongue, thickening of the oral mucosa, tooth impressions on the lateral and anterior margins of the tongue, and excessive saliva production.5

**DIAGNOSING ACROMEGALY**

Once acromegaly is suspected, diagnosis is straightforward. The criterion standard for diagnosing acromegaly is elevated GH levels. However, because of an individual’s sporadic secretion of GH throughout the day, random GH measures are not useful. Acromegaly is diagnosed under conditions when GH is normally suppressed, thus the oral glucose tolerance test (OGTT) is used, in the same way it is used to test for diabetes. After an overnight fast, the patient ingests 80 g of an oral glucose solution over a 5-minute period; serum GH levels are obtained at intervals of 0, 30, 60, 90, and 120 minutes. GH levels in normal persons should suppress to below 1 ng/mL. If the GH levels do not fall to that level, acromegaly is strongly suggested and a magnetic resonance imaging (MRI) examination should be performed to locate the tumor and confirm the diagnosis. If no pituitary tumor is found, tumors in the chest, abdomen, or pelvis also can cause excess GH through direct production or excess production of GHRH; these conditions also should be considered and evaluated. As Marie Cook, RN, BSN, will discuss in this monograph, patient education is critical—even before a firm diagnosis is made. When the possibility of acromegaly is suspected and an MRI examination is ordered, the physician must reassure the patient that acromegaly is not “brain cancer.”

Measuring serum IGF-1 levels may also be adequate for the initial screening of GH excess; IGF-1 levels are normally stable over the course of the day. An elevated serum IGF-1, in the appropriate clinical setting, is adequate for the diagnosis of acromegaly. However, IGF-1 also can be elevated during pregnancy or puberty but may be lower in older patients or in those patients with type 2 diabetes mellitus, thus it is important for clinicians to compare these findings with age-normalized and gender-normalized values. Other conditions can also affect IGF-1 levels, such as nutritional status, liver dysfunction, insulin levels, and illness.

**TREATMENT OPTIONS FOR ACROMEGALY**

Although a diagnosis of acromegaly can be devastating, many patients are relieved to find out the cause...
of their uncomfortable and often disfiguring changes. There are several treatment options available, which will be outlined below.

The treatment goals for acromegaly are 5-fold (Table 1): normalize disease markers (i.e., reduce GH to normal levels and normalize IGF-1 levels to age-matched and sex-matched levels); relieve the pressure of the growing tumor on surrounding brain areas by ablating or reducing tumor size; preserve normal pituitary function; reverse or ameliorate the symptoms of acromegaly, especially the cardiovascular, pulmonary, and metabolic abnormalities; and restore the patient’s life expectancy to that of the general population. The normalization of GH and IGF-1 levels reverses the mortality risk associated with acromegaly and is associated with improving morbidity.6 The definition of a “cure” is controversial but is generally agreed to include serum IGF-1 levels within the reference range and the reduction of GH to less than 1 ng/mL after OGTT.7,8 Some healthcare providers advocate the use of the term “control of disease” rather than “cure.”

Several years ago, a consortium of 68 leading neuroendocrinologists and neurosurgeons worldwide created consensus guidelines on the management of acromegaly.9 Currently, 3 types of treatment are available: surgery, pharmacotherapy, and radiation. Each modality has its own advantages and disadvantages and must be tailored to the patient.

Surgery

After a patient has received a confirmed diagnosis, treatment begins with transsphenoidal surgery to debulk the tumor. Craniotomy is rarely indicated. Microadenomas are much easier to completely resect than larger tumors. The goal of surgery with pituitary macroadenomas is to debulk the tumor, rather than remove it completely because, frequently, the tumor has invaded other tissues or has grown so large that complete resection would risk damage to surrounding nerves or tissues. Debulking the tumor increases the chances of success with follow-up adjuvant therapy.

Cure rates with surgery are high; treatment success is measured by GH and IGF-1 levels taken at 2 to 4 months after surgery.9 GH levels can be brought into the reference range in approximately 90% of patients with well-defined microadenomas; because resection of macroadenomas is more complicated, published cure rates with macroadenomas range from 45% to 65%.10-13 Successful transphenoidal surgery also significantly improves some cardiac and metabolic parameters and slightly reduces systolic blood pressure levels in patients with acromegaly.14,15 Cure rates also depend on tumor location, extension, and the surgical experience of the individual surgeon.9,12 Complications occur infrequently and can include mortality, visual impairment, meningitis, cerebrospinal fluid leakage, permanent anterior lobe deficits, diabetes insipidus, and local nasal complications. Contraindications for transphenoidal surgery include frailty, physical illness, or comorbidity, but pretreatment with a somatostatin analog (described below) can be offered for those patients with an unacceptable anesthesia risk (i.e., cardiomyopathy, cerebrovascular disease, or chronic obstructive pulmonary disease).16 However, there are no available data that address whether pretreatment with a somatostatin analog will improve the efficacy of surgery. In those cases in which disease persists, reoperation is not usually effective, thus pharmacotherapy is recommended as a second-line treatment.8,9

Pharmacotherapy

There are 3 types of drugs to treat acromegaly (Table 2): somatostatin analogs, dopamine agonists, and GH receptor antagonists. Their characteristics are summarized in Table 3.

Somatostatin analogs (octreotide and, in Europe, lanreotide in addition to octreotide) are the mainstay of acromegaly pharmacotherapy. These drugs bind to somatostatin receptors in the pituitary that control GH secretion (SSTR2).17 Somatostatin analogs can be administered by subcutaneous or intramuscular injection, and the long-acting forms are preferred over the

<table>
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<th>Table 1. Goals of Acromegaly</th>
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<tr>
<td>• Normalize biochemical disease markers</td>
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<td>• Control tumor mass without harming normal pituitary function (treatment options have differential efficacy and risks of pituitary dysfunction)</td>
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<tr>
<td>• Relieve signs and symptoms</td>
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<td>• Restore life expectancy to that of the general population</td>
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shorter-acting versions, as Marie Cook, RN, BSN, will
discuss elsewhere in this monograph.18,19

Somatostatin analogs control GH axis parameters
in 50% to 70% of cases; more than 50% of patients
achieve serum levels less than 2.5 ng/mL, and almost
75% of patients have IGF-1 levels in the reference
range.20 These analogs also are able to shrink a subset
of tumors mildly (20%–40% decrease), usually within
3 months of therapy.20-22 Therefore, somatostatin
analsogs may be efficient at controlling GH secretion
but are less capable of shrinking the tumor mass.

Some studies suggest that these agents are also
able to reduce or eliminate some of the clinical symp-
toms and signs of acromegaly, such as headache,
swelling, enlarged tongue, sleep apnea, and increased
joint size.23-25 Thus, these drugs can address 4 goals of
therapy: reducing the signs and symptoms of
acromegaly, controlling the adenoma, normalizing
biochemical markers, and mortality. The adverse
effects with somatostatin analogs are usually gas-
trointestinal symptoms (diarrhea and abdominal
pain), which often attenuate with long-term treat-
ment. The most frequent adverse effects are gall-
stones. Even if the stones become large, which occurs
in approximately 30% to 40% of patients, they do
not commonly become clinically symptomatic.
Diarrhea, nausea, abdominal pain, and abdominal
discomfort, in my experience, are more prevalent in
patients who are receiving subcutaneous octreotide 3
times daily than with the long-acting depot formulations.
With the long-acting depot formulations,
symptoms, if they occur, are often limited to the first
48 to 72 hours after the injection. Hyperglycemia,
because of insulin inhibition, can occur but is highly
variable from patient to patient.

DOPAMINE AGONISTS

Although dopamine is one of the neurotransmit-
ters that increases GH secretion, dopamine agonists
are sometimes able to reduce GH secretion by ade-
nomas, and they have been used as a second-line
therapy, if disease persists after surgery. The
dopamine agonist bromocriptine is effective only in
approximately 10% of patients with acromegaly and
high doses are often required, thus increasing the
risk of adverse events. The dopamine agonist caber-
goline may be more effective, as reported in up to
39% of patients in one study.27 Cabergoline is more
effective with the less active form of acromegaly and
in patients with coexisting hyperprolactinemia.
Dopamine agonists can be used in combination with
somatostatin analogs to increase chances of efficacy.28

GROWTH HORMONE RECEPTOR ANTAGONISTS

A growth hormone receptor (GHR) antagonist called
pegvisomant is one of the newer agents to be approved
for treating acromegaly. A GHR antagonist constitutes a
novel approach to treatment by blocking all peripheral
effects of GH, resulting in decreased production of IGF-
1, locally and at the liver. GHR antagonists can be used
in patients who do not respond to somatostatin analogs
or other types of treatment or may be considered as a
first-line therapy in selected patients, such as patients
with intrasellar tumors or diabetes mellitus.

Growth hormone receptor antagonists appear to be
highly efficacious, with normalization of IGF-1 in up to

| Table 2. Current Pharmacotherapeutic Options
for Acromegaly |
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<td><strong>Somatostatin analogs</strong></td>
<td>Octreotide</td>
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<td><strong>Dopamine agonists</strong></td>
<td>Bromocriptine, Cabergoline</td>
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<td><strong>Growth hormone antagonist</strong></td>
<td>Pegvisomant</td>
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| Table 3. Comparison of Medical Therapies for
Acromegaly |
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<tr>
<td>Somatostatin analogs</td>
<td>Normalize IGF-1 in more than 60% of patients</td>
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<tr>
<td>Tumor shrinkage in some patients (modest)</td>
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<tr>
<td>Glycemic control concerns</td>
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<tr>
<td>Dopamine agonists</td>
<td>Require very high doses</td>
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<tr>
<td>Minority of patients respond</td>
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<tr>
<td>GHR antagonists</td>
<td>Normalizes IGF-1 in almost all patients</td>
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<tr>
<td>Improved glycemic control?</td>
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<tr>
<td>Does not treat tumor</td>
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<tr>
<td>No long-term data</td>
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GHR = growth hormone receptor; IGF-1 = insulin-like growth factor-1.
97% of patients and a reduction in a patient's ring size by up to 2 whole sizes. In patients treated with a GHR antagonist, GH levels may increase (Figure 2). The potential adverse events with GHR use include an increase in tumor size, as seen in 2 published reports (Figure 3), but the overall risk from these changes is unclear. Other safety concerns with pegvisomant include antibody formation (but there is no evidence of significant antibody titer nor tachyphylaxis) and abnormal but reversible liver tests (2 of 158 patients). Pegvisomant is a highly effective therapy for acromegaly and is well tolerated overall by patients. The clinical experience with this agent is limited; as further studies are performed, guidelines may define more clearly the role of pegvisomant in the management of acromegaly.

**ANTIDEPRESSANT AND ANTIANXIETY MEDICATIONS**

There is no clear relationship between excess GH and depression or anxiety, but clearly the morbidity and mortality with acromegaly affects a patient’s quality of life. The influence of hormonal disturbances with acromegaly in the development of depression should be individually evaluated. Antidepressants may be warranted at different periods throughout the treatment process and psychotherapy should be part of a comprehensive management approach. Because acromegaly is a lifelong disease, these patients face lifelong challenges.

**RADIATION**

Radiation is no longer considered to be the mainstay of therapy for acromegaly not cured by surgery. Indications for radiation include the failure to normalize biochemical parameters with medical therapy, inability of patients to sustain the cost or duration of long-term medical therapy, or the prior existence of hypopituitarism. Radiotherapy increases the risk of hypopituitarism (60% in 5–10 years), which also could affect a patient’s fertility. There is also a potential for optic nerve damage, depending on the tumor location. Advances in stereotactic techniques have helped to more definitively target the tumor and reduce damage to surrounding healthy tissues. Radiotherapy results in a slow decline in GH and IGF-1, with the greatest decline seen in patients within the first 2 years after treatment. Radiotherapy is viewed as an adjunctive treatment to surgery and somatostatin analogs.

**MONITORING THERAPY**

Each therapy for acromegaly is monitored in 4 ways: GH and IGF-1 levels, tumor size, visual fields, and signs and symptoms. Healthcare practitioners with frequent patient contact should ask their patients about symptoms (Are the headaches improving? Are the issues regarding sleep improving? Is the joint pain improving?)

**Figure 2. Growth Hormone and Insulin-like Growth Factor-1 Changes with Pegvisomant Treatment**

![Graph showing changes in GH and IGF-1 levels with pegvisomant treatment.](image)

**Figure 3. Tumor Volume Changes in 92 Patients Receiving Daily Pegvisomant for More Than 6 Months**

![Graph showing tumor volume changes over time.](image)

GH = growth hormone; IGF-1 = insulin-like growth factor-1.

Two patients from this study experienced progressive growth of their pituitary tumors.
RT = radiation therapy.
Reproduced with permission from van der Lely et al. Lancet. 2001;358:1754-1759.30
because these benefits may not correlate necessarily with changes in biochemical indices.

**Proposed Therapeutic Guidelines**

By the time they are diagnosed, most patients with acromegaly are desperate for a treatment to reverse the course of this disorder. The most recent guidelines from the American Association of Clinical Endocrinologists (AACE) are now available (www.aace.com/clin/guidelines/). As shown in Figure 4, these guidelines suggest use of somatostatin analogs as initial medical therapy for active acromegaly. Although not depicted in this figure from the AACE guidelines, it is certainly reasonable to consider use of a dopamine agonist as first-line medical therapy or use of a GH receptor antagonist as first-line therapy in selected patients. Treatment cost can be an issue for some patients because this is a lifelong disease, but resources are available to assist with payment (as discussed by Marie Cook, RN, BSN, in this monograph). The exact role of pegvisomant remains to be defined, and treatment strategies should be tailored to individual patients.

**Conclusions**

Acromegaly is a rare but severe disorder, causing not only significant disfigurement but also metabolic changes that increase mortality. Unfortunately, because of its insidious and seemingly benign onset, the diagnosis of acromegaly usually occurs up to 10 years after symptom onset. By this time, many of the physical changes associated with the disorder have become apparent and are distressing to the patient. The clinician’s recognition and diagnosis of acromegaly in the earlier stages can help to avoid some of these problems for patients. Primary care practitioners in numerous medical specialties (e.g., obstetrics, family medicine, dentistry) have the most frequent and regular contact with patients, thus they are in the best position to identify acromegaly or at least include acromegaly in the differential diagnosis of unexplained patient signs and symptoms. With the array of treatment options now available, clinicians can provide hope to patients with acromegaly regarding their quality of life and life expectancy—underscoring the importance of understanding this disease.

**References**


