CME CREDIT

TAKE-HOME POINTS FROM EDUCATIONAL PRESENTATIONS BY CLEVELAND CLINIC FACULTY AND VISITING PROFESSORS

New options for diagnosing and treating acromegaly

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ABSTRACT

Insulin-like growth factor 1 (IGF-1) is the final pathway of the growth hormone cascade, and is a better clinical measure of acromegaly than growth hormone itself. In patients with acromegaly, medical treatment with a somatostatin analog normalizes growth hormone and IGF-1 levels and produces clinical improvement quickly.

ACROMEGALY, caused by an overproduction of growth hormone, was once diagnosed primarily by the physical changes it produces, followed by measurement of growth hormone. Now, a more complete understanding of the growth hormone cascade has shown that insulin-like growth factor 1 (IGF-1) is a sensitive clinical marker of the severity of acromegaly. In addition, two somatostatin analogs (eg, octreotide, lanreotide) are now available as medical treatment.

EPIDEMIOLOGY OF ACROMEGALY

Acromegaly is a classic endocrine disorder. Indeed, growth hormone was the first pituitary hormone identified.

Acromegaly occurs in 3 to 4 persons per million per year. It is equally frequent in both sexes. The mean age at diagnosis is 40 years in men and 45 years in women.

This disease confers a mortality rate two to three times higher than in healthy persons. The mean age at death is approximately 60 years. Deaths are primarily due to vascular disorders (eg, cardiomyopathy) and various cancers.

PHYSIOLOGY OF ACROMEGALY

Two hypothalamic hormones regulate growth hormone:

Growth hormone-releasing hormone (GHRH) stimulates the synthesis and release of growth hormone from the pituitary gland.

Somatostatin inhibits release of growth hormone, but not its synthesis (FIGURE 1).

When growth hormone is released into the peripheral circulation, it stimulates the production of IGF-1—the true growth hormone—by the liver and other organs. Growth hormone also has independent metabolic effects on lipids and glucose.

Most cases of acromegaly are due to pituitary adenomas. However, a few are due to ectopic GHRH-secreting tumors.

IGF-1 is the true growth hormone

In a study that provides insight into how pituitary adenomas develop, Thapar et al[1] found that they express the gene for GHRH. The amount of GHRH mRNA present was proportionate to the tumor's size, proliferating ability, and invasiveness, and to the amount of growth hormone it secreted. Further, the amount of GHRH mRNA was the single most important factor that predicted the likelihood of a cure. In effect, pituitary adenomas can stimulate themselves to grow and secrete growth hormone.

DIAGNOSING ACROMEGALY

Acromegaly is suspected on the basis of the classic clinical signs and symptoms (TABLE 1).

The characteristic appearance of persons with acromegaly identifies the condition at a glance: enlarged hands and feet, oily skin, thick lips, a protruding jaw. In uncertain cases, ask the patient to bring in his or her photo album. Often, one can pinpoint the year of onset by comparing pictures from different years.

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Examination may reveal some of the complications of acromegaly: thyroid hypertrophy, cardiomegaly, hepatomegaly, splenomegaly, nephromegaly, hypertension, and osteoarthritis. If the tumor impinges on the optic chiasma, the patient may have visual field defects.

MRI scanning usually reveals a macroadenoma, often quite large. There is a rough correlation between size of tumor and levels of growth hormone.

Growth hormone levels may be misleading. Normally, growth hormone is mostly secreted during sleep in pulses approximately 2 hours apart, and it has a short half-life. Thus, serum levels fluctuate widely through the day. Growth hormone levels may be above the normal limit during pulses of secretion in normal persons; conversely, they may be within the stated normal range between pulses in persons with acromegaly.

IGF-1 levels are the single best tool for diagnosing and monitoring acromegaly, because plasma levels remain steady through the day and night. The normal range for IGF-1 varies among laboratories and is sex-dependent and age-dependent. An elevated IGF-1 level nearly always indicates that the growth hormone level is elevated. However, IGF-1 increases with growth hormone only up to a growth hormone level of approximately 20 ng/mL, and reaches a plateau thereafter. Therefore, an elevated IGF-1 level does not distinguish between a growth hormone level of 500 or 50.

Of note: nearly everyone has high IGF-1 levels during puberty and pregnancy.

Dynamic tests are cumbersome and unreliable and not usually needed to diagnose acromegaly, but they may be useful after surgery to determine if the tumor is still active. Examples of dynamic tests:

- Oral glucose (75–100 g) suppresses growth hormone levels to less than 2 µg/L in normal subjects, but not in persons with acromegaly.
- Thyrotropin-releasing hormone (TRH) injection has no effect on growth hormone in normal subjects, but increases growth hormone by more than 50% in 60% to 80% of persons with acromegaly.
- Bromocriptine suppresses growth hormone in 50% of persons with acromegaly.

Physiology of growth hormone secretion

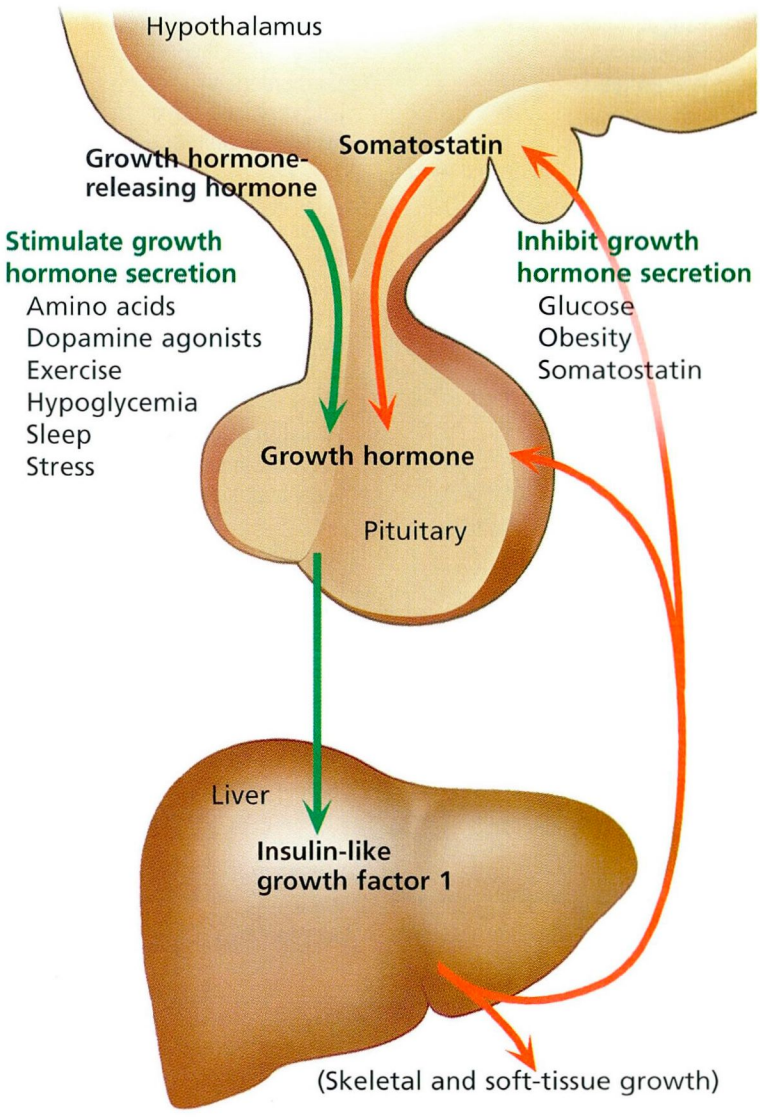

FIGURE 1

GHRH assays are usually not needed. However, a few persons have acromegaly caused by oversecretion of GHRH by the hypothalamus or from ectopic tumors. In such patients, the histologic study of the excised tissue might show pituitary hyperplasia but not the tumor. Plasma GHRH should be measured in every acromegalic person who has evidence of another, extrapituitary tumor (eg, in a lung, the pancreas, or an adrenal gland).

TABLE 1

Signs and symptoms of acromegaly

General
- Fatigue
- Heat intolerance
- Weight gain

Skin structures
- Acral growth (hands and feet)
- Doughy and oily skin
- Skin tags
- Coarsening of facial features
- Hypertrichosis
- Hyperhidrosis
- Acanthosis nigricans
- Lipomata
- Hyperpigmentation

Head and neck
- Headaches
- Goiter
- Frontal bossing
- Parotid enlargement
- Prognathism

Eyes
- Visual field defects
- Papilledema

Nose, throat, and sinuses
- Sinus congestion
- Enlarged tongue
- Malocclusion
- Voice change
- Sleep apnea
- Rhinorrhea

Cardiopulmonary
- Congestive heart failure
- Arrhythmias, hypertension
- Cardiomegaly
- Left ventricular hypertrophy
- Restrictive pulmonary disease

Genitourinary
- Decreased libido
- Erectile dysfunction
- Oligomenorrhea
- Infertility
- Nephrolithiasis

Gastrointestinal
- Cholelithiasis
- Hepatosplenomegaly
- Colonic polyps, cancer

Neurologic
- Paresthesias
- Carpal tunnel syndrome
- Seizures

Endocrinologic
- Glucose intolerance
- Diabetes mellitus
- Hypolipidemia
- Pituitary apoplexy

Musculoskeletal
- Weakness
- Proximal myopathy
- Arthralgias
- Osteoporosis
- Osteoarthritis

SOURCE: ADAPTED FROM MAUGANS TA, COATES ML. DIAGNOSIS AND TREATMENT OF ACROMEGALY. AMERICAN FAMILY PHYSICIAN 1995; 52:207–213.

TREATING ACROMEGALY

A preliminary, retrospective study showed that treatment of acromegaly normalizes the mortality rate—but only if the growth hormone level can be reduced to less than 2.5 ng/mL.[2] Even if this goal cannot be achieved, however, treatment can alleviate the symptoms of this painful and unpleasant disease.

There are three modalities of therapy: surgery, radiotherapy, and medical therapy.

Surgery

Ross and Wilson[3] reviewed a series of 214 of their own surgical patients and 1,360 cases reported in the literature. Surgical complications occurred in 7% to 20% of patients, and hypopituitarism occurred in 5% to 18%. Growth hormone levels fell to less than 5 ng/mL in 56% of their own patients, and 60% in the other patients. However, the few studies to date that looked at IGF-1 levels, which we now know is the best parameter to follow, found success rates of only 20% to 30%.

Radiotherapy

Radiotherapy is often used when surgery fails to lower the growth hormone level to the normal range. This therapy takes time to work. In a series of 46 patients, Feek et al[4] found that the growth hormone level fell by approximately 50% in the first few years after radiotherapy, and then by about 14% per year up to 20 years.

Approximately 50% of patients achieve growth hormone levels less than 5 ng/mL 10 years after starting radiotherapy. Fewer patients achieve a normal IGF-1 level: at our institution, only 2 of 38 patients achieved normal IGF-1 levels with radiotherapy.

Hypopituitarism is the most common complication, occurring in 40% to 50% of patients after 5 years. Other side effects are visual impairment, necrosis of brain tissue, and increased risk of brain malignancy.

Medical therapy

Two classes of drugs are used in acromegaly: dopamine agonists (eg, bromocriptine) and somatostatin analogs (eg, octreotide, lanreotide).

Dopamine agonists. In a review of 31 clinical trials, Jaffe and Barkan[5] found that the dopamine agonist bromocriptine, in doses of 7.5 to 80 mg/day, lowered growth hormone levels to less than 10 ng/mL in 287 of 543 patients, and to less than 5 ng/mL in 115. Normal IGF-1 levels were achieved in approximately 10%.

Somatostatin analogs are highly effective, reducing growth hormone concentrations to less than 5 ng/mL in more than half of patients and normalizing IGF-1 levels in approximately 70%.[6] They also work rapidly, often causing soft-tissue regression within 48 hours of starting therapy. Another advantage: they are the only medications that address acromegaly due to ectopic GHRH production.

A disadvantage of currently available preparations is that they must be given by injection three times per day. Long-acting formulations of octreotide and lanreotide are being developed.

A mutant form of growth hormone, which occupies the growth hormone receptor but is physiologically inactive, is also under development.

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