

Patient information: Acromegaly (somatotroph adenomas)

Shiomo Melmed, MD

University of California at Los Angeles School of Medicine

Peter] Snyder, MD

University of Pennsylvania School of Medicine

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Acromegaly is the clinical syndrome that results from prolonged, excessive secretion of growth hormone (GH). It is characterized by the overgrowth of almost all tissues and is manifested most obviously by coarsening of facial features and an increase in the size of the hands and feet. Acromegaly is uncommon; only three to four cases are diagnosed per million people each year. It develops so gradually that it goes unrecognized for many years before the diagnosis is made.

The most common cause of acromegaly is a benign tumor (adenoma) of the somatotroph cells (those that produce growth hormone) of the anterior pituitary gland, which is located in the middle of the head just below the brain.

Acromegaly can lead to serious illness and even death if it is not treated successfully, but treatment that lowers growth hormone to normal leads to a normal life span.

CLINICAL FEATURES OF ACROMEGALY – The clinical features of acromegaly result from excessive production of growth hormone, which stimulates excessive production of another hormone, called insulin-like growth factor-i (IGF-i). IGF-i, in turn, causes most of the manifestations of acromegaly by causing the growth of virtually all tissues of the body. One exception is the length of the bones of the arms and legs, which do not get longer after the bone growth centers close during middle or late puberty. Other features of acromegaly can be the result of the size of the pituitary adenoma and its compression of nearby structures.

Features due to excessive growth hormone – The best recognized features of acromegaly occur due to excessive growth of soft tissue, cartilage, and bone in the face, hands and feet. The facial features (nose, lips, ears, and forehead) become coarse, the tongue enlarges, the space between the teeth increases, and the lower jaw grows, resulting in an underbite and extended lower jaw. The hands and fingers swell, necessitating increased size of rings and gloves. The feet enlarge, often necessitating shoes of a larger length and width.

The skin may thicken, and skin tags may appear. Excessive sweating at rest is common. Facial hair growth increases, which women especially notice.

Excessive soft tissue growth of the throat and voice box can lead to a hoarse voice

and, more importantly, sleep apnea. Sleep apnea is a condition in which a person does not breathe for several seconds at a time during sleep. As a consequence, insufficient oxygen gets into the blood stream during sleep, and the sleep is not normally refreshing. The result is daytime sleepiness, sometimes to the degree that the person falls asleep while driving.

Overgrowth of wrist soft tissues can press on nerves to the hands and lead to tingling or pain in the fingers, called the carpal tunnel syndrome. Overgrowth of the ends of bones can lead to damage to neighboring cartilage and thereby to a type of painful arthritis called osteoarthritis.

Heart disease is increased in acromegaly. One probable cause is enlargement of the heart muscle, which may cause impaired functioning of the muscle, called cardiomyopathy. Another is high blood pressure, which is common in acromegaly. Occasional patients have problems with their heart valves.

Acromegaly may be associated with an increased risk of benign and malignant tumors if growth hormone levels are left uncontrolled. Benign tumors of the uterus called fibroids are more common in acromegaly, and patients also are more likely to have polyps of the colon, which may become cancerous if not surgically removed.

Higher blood sugar is one consequence of acromegaly that may be a direct result of excessive growth hormone production, which causes increased resistance to the action of insulin. As a result, higher doses of diabetic medications are required by known diabetics, or diabetes may become apparent in those not previously known to be diabetic.

The mortality rate in acromegaly is two to three times the expected rate, mostly due to cardiovascular disease. Average survival in acromegaly is reduced by approximately 10 years. Decreased survival is more likely when the growth hormone is higher and when diabetes is also present. If treatment lowers growth hormone to normal, mortality is restored to normal.

Features due to the size of the somatotroph adenoma If the somatotroph adenoma becomes large enough, eg, 2 centimeters (about 1 inch) or more in diameter, it may cause abnormalities by its size alone.

If the adenoma grows upward sufficiently, it may stretch the nerves that go to the eyes (optic chiasm) to the degree that vision, especially peripheral vision, is impaired.

Pressure on the normal pituitary gland can impair production of the hormones that control the thyroid gland, adrenal glands, and the ovaries in women and testes in men, leading to underactivity of these glands.

DIAGNOSIS OF ACROMEGALY –After acromegaly is suspected by a person's appearance, the diagnosis must be confirmed by demonstrating that the blood concentrations of IGE-1 and/or growth hormone are higher than normal.

The blood concentration of IGE-1 can be determined in a single blood specimen at any time of day, but the concentration of growth hormone must be determined in several specimens of blood drawn before and after drinking a glucose (sugar)

solution. The concentration in a non-acromegalic person will fall below a certain level (1 ng/mL), but the concentration in a person who has acromegaly will not.

Once excessive growth hormone secretion has been confirmed, magnetic resonance imaging (MRI) should be performed to determine if there is an abnormality in the pituitary suggestive of an adenoma.

TREATMENT OPTIONS FOR ACROMEGALY Because the mortality rate in untreated acromegaly is greater than normal, most patients with acromegaly should be treated, even those who have no symptoms and those whose clinical status seems stable. The goal of therapy is to lower the blood growth hormone concentration to less than 1 ng/mL after a glucose ingestion. If therapy is successful in doing so, the soft tissue changes will regress within several months and the mortality rate will return to normal. Sometimes, however, the initial treatment is not entirely successful, so additional treatment is needed.

There are three main forms of treatment:

- Surgery
- Medications
- Radiation

Surgery –Surgery is the only treatment that offers the chance of a cure, by removing all of a somatotroph adenoma, but the chance of complete removal is high only when the adenoma does not extend outside the normal boundaries of the pituitary. In such a situation, surgery is often the first choice of treatment. Another situation in which surgery is the first choice of treatment is when the adenoma is very large and impairing or threatening vision.

Once the choice of surgery has been made, the next step is identifying a neurosurgeon who has had extensive experience in transsphenoidal surgery. The more experience the surgeon has had in this procedure, the more likely is the surgery to be successful, both in removing the greatest amount of adenoma tissue and in avoiding postoperative complications.

Surgery is usually performed through an incision in the nose that is extended back through the sphenoid sinus (hence, the procedure is called transsphenoidal surgery) and then through a bone that is both the roof of this sinus and the floor on which the pituitary sits. Sometimes an endoscope is also used for better visualization in order to determine if all of the adenoma has been excised.

Efficacy –Surgery is usually effective in reducing the blood growth hormone concentration at least to some degree, but less often effective in reducing it entirely to normal. The chance that the growth hormone concentration will be normal after surgery is directly related to the size of the adenoma before surgery. When transsphenoidal surgery for acromegaly is performed by a neurosurgeon who has great experience with this procedure, 80 percent of people with adenomas less than 1 cm (one-half inch) in diameter experience a fall in blood growth hormone and IGE-1 to normal, but if the adenoma is much larger and extending beyond the normal bounds of the pituitary, 30 percent or fewer will experience such a fall to normal.

If the adenoma is completely excised, the blood GH concentration falls to normal within hours after surgery and the blood IGE-1 concentration falls to normal in days to months.

Complications –Serious complications are uncommon when the procedure is performed by a neurosurgeon who has considerable experience performing transsphenoidal surgery. The chance of serious complications – such as worsening of vision, hormonal imbalance, meningitis, nasal leakage, or very rarely, death – is less than 5 percent when the procedure is performed by a neurosurgeon who has performed more than 500 transsphenoidal operations but 15 to 20 percent when performed by a neurosurgeon who has performed fewer than 200 of these procedures. The chance of damage to the normal pituitary gland (so that one or more pituitary hormones is not produced normally) is about 7 percent for the most experienced surgeons and 20 percent for the least. These deficiencies can lead to underactivity of the thyroid gland, adrenal glands, and the ovaries in women and testicles in men.

Medications –There are three classes of medications used to treat acromegaly now:

- Somatostatin analogs (octreotide or lanreotide)
- Dopamine agonists, especially cabergoline
- Growth hormone receptor antagonist (pegvisomant)

Somatostatin analogs –Somatostatin analogs inhibit growth hormone secretion by the somatotroph cells of the pituitary. Both octreotide (Sandostatin and Sandostatin [AR]) and lanreotide (not available in the US) are made in short- acting and long-acting forms. The short-acting forms are given several times a day by injection just under the skin, and the long-acting forms are given every two or four weeks by an injection into the muscle or under the skin. These medications can be used as primary treatment, especially when an adenoma is too large to resect entirely, although not if vision is significantly impaired. They can also be used as secondary treatment, especially when residual adenoma tissue remains and the blood growth hormone concentration is still elevated after transsphenoidal surgery.

Efficacy –Somatostatin analogs reduce blood concentrations of growth hormone and IGE-1 to some degree in a majority of patients with acromegaly and to normal in about 60 percent overall. The long-acting forms are as effective as the short- acting forms. The effect of these analogs in reducing adenoma size has not been studied as well, but so far a reduction in size has been shown in about 25 percent of patients.

Side effects –Somatostatin analogs are usually well-tolerated, but there are some side effects. Common side effects include

- Abdominal cramps, abdominal discomfort, bloating, and loose stools during the first week or two of treatment, especially with the short-acting preparations. These symptoms usually remit spontaneously when treatment is continued.
- Gallstones, which develop within the first six months of treatment in about 20 percent of those who take these medications. Development of gallstones does not necessitate discontinuing treatment, but in the small percentage of persons in whom the gallstones cause symptoms, the gallbladder may have to be surgically removed.

Dopamine agonists –These are synthetic compounds that act like the naturally occurring compound dopamine and are therefore called dopamine agonists. They may inhibit growth hormone secretion and therefore the blood IGE-1 concentration in people who have acromegaly. Because they can be taken orally, they are more convenient than other forms of treatment.

Efficacy –Cabergoline is the dopamine agonist that appears to be most effective in lowering the serum growth hormone concentration. Some studies in the medical literature report that cabergoline reduces the blood concentrations of growth hormone and IGE-1 to normal in one-third of patients with acromegaly, but most endocrinologists find a lower rate of success. Nonetheless, it is a boon to any person who has a good result, because it can be taken orally and usually has few, if any, side effects. Bromocriptine appears to be much less effective and probably should not be used.

Side effects –The most common side effects of dopamine agents are

- Nausea. Cabergoline is much less likely to cause this side effect than bromocriptine.
- Lightheadedness on standing due to a fall in blood pressure
- Mental foginess
- Baldness or mood disturbances

Side effects, especially nausea, can be minimized by taking the medication with meals or at bedtime and beginning with the lowest dose and increasing the dose gradually.

Growth hormone receptor antagonist –A new type of medication has been developed that blocks the effect of growth hormone by binding to its peripheral tissue receptor, which decreases IGE-1 production and thereby decreases growth effects. This medication, called pegvisomant, decreases the blood concentration of IGE-1 to normal in 90 percent of patients with acromegaly who receive the largest dose by daily subcutaneous injection. Although no direct comparisons of pegvisomant have yet been reported, anecdotally it appears to be effective in lowering the serum IGE-1 concentration to normal even in many patients in whom surgery, radiation, and other medications were not successful.

Radiation therapy –Radiation therapy has been used for many years for treatment of pituitary adenomas, including somatotroph adenomas causing acromegaly. Several forms of radiation are now available, including the form available for decades, called conventional radiation. New high-energy forms of radiation therapy are referred collectively as radiosurgery, although little if any surgery is involved. One of these, which uses gamma radiation, is called gamma knife.

Efficacy –Radiation therapy is usually effective in stopping or even reversing adenoma growth and in decreasing growth hormone and IGE-1 production, but the decline in growth hormone secretion (and clinical improvement) is very slow. Even 10 to 15 years after radiation, a minority of patients achieve a normal blood growth hormone concentration.

Side effects –Side effects that occur during or shortly after treatment include fatigue, nausea, loss of scalp hair, and loss of taste and smell. These usually remit within weeks to months. Damage to a nerve that controls vision (optic neuritis), resulting in blindness, usually in one eye, can occur in 6 to 24 months. It is very rare but permanent. Accelerated blood vessel disease (hardening of the arteries) can occur several years later and can cause stroke. Within 10 years after treatment, about 50 percent of patients treated with pituitary radiation develop a deficiency of one or more pituitary hormones, including the hormones that control the thyroid gland, adrenal glands, and ovaries or testicles.

PREGNANCY AND ACROMEGALY –Little is known about the interaction between acromegaly and pregnancy, although it appears that pregnancy usually carries to term. At present, reasonable guidelines concerning pregnancy are

- Consult your endocrinologist prior to deciding on pregnancy.
- Stop any medication to treat acromegaly when pregnancy is confirmed.
- Monitor visual fields during pregnancy in persons who are known to have adenomas larger than 1 cm (one-half inch) in diameter, but reserve MRI evaluation for those with clearly demonstrated impairment of vision.

LONG-TERM MANAGEMENT OF ACROMEGALY –Whatever treatment is chosen initially, the results should be monitored long term. Monitoring should be done in the following areas:

Clinical manifestations of acromegaly –The patient with acromegaly should notice whether or not treatment improves the symptoms, such as headache. The patient and the physician should notice whether or not treatment improves the outward manifestations of acromegaly, such as soft tissue enlargement of the face, hands, and feet. Until the blood concentrations of growth hormone and IGE-1 return to normal, patient and physician should be vigilant about treating sleep apnea, if present, and a colonoscopy should be performed every few years to detect (and if necessary, remove) colonic polyps.

Blood concentrations of growth hormone and IGF-1 .The blood concentration of growth hormone after ingestion of a glucose solution and/or the blood concentration of IGE-1 at any time should be measured to determine if they are controlled. These are the best objective tests to determine if treatment has been successful. Success means that the blood growth hormone after ingesting glucose is less than 1 ng/mL and the IGE-1 concentration is within the range of normal for a person's age.

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Blood concentrations of other pituitary hormones –If the treatment is surgery or radiation, the production of hormones produced by the normal pituitary gland could be decreased. Any deficiencies of the hormones made by the thyroid gland, adrenal glands, and ovaries or testes should be replaced.

Size of the adenoma –If the adenoma was initially larger than 1 cm (one-half inch), it is important to determine by magnetic resonance imaging if treatment has decreased its size.

If monitoring indicates that the initial treatment has not been entirely successful, additional treatment should be strongly considered. Longterm monitoring should then continue to determine if the additional treatment is successful.

WHERE TO GET MORE INFORMATION –Your doctor is the best resource for finding out important information related to your particular case. Not all patients with acromegaly are alike, and it is important that your situation is individually evaluated by someone who knows you as a whole person.

This discussion will be updated as needed every four months on our web site (www.uptodate.com). Additional topics as well as selected discussions written for health care professionals are also available for those who would like more detailed information.

Several other internet sites also have information about acromegaly. Information provided by the National Institutes of Health, national medical societies, and some other well-established organizations are often reliable sources of information, although the frequency with which their information is updated is variable.

- National Library of Medicine
(<http://www.nlm.nih.gov/medlineplus/>)

- The National Institute of Diabetes and Digestive and Kidney Disorders (the branch of the National institutes of Health concerned with hormonal and endocrine disorders)
<http://www.niddk.nih.gov/>)

- The Hormone Foundation
(<http://www.hormone.org>)
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