Approximately, 30% of GH-secreting pituitary adenomas are plurihormonal and also secrete prolactin. The incidence of acromegaly is about 2 to 4 per million population, and the mean age at diagnosis is 40 to 50 years.

### Pathology

GH-secreting tumors are caused by a clonal expansion of pure somatotrophs or mixed somatomammotrophs. A variety of genetic abnormalities can be found in GH-secreting pituitary adenomas. GH hypersecretion due to somatotroph hyperplasia and adenomas is also seen in patients with McCune-Albright syndrome, which is caused by a G protein–activating mutation. There are also familial syndromes associated with GH-secreting pituitary adenomas, including multiple endocrine neoplasia type 1, Carney complex (myxomas, skin pigmentation, and testicular, adrenal, and pituitary tumors) and mutations in AIP (aryl hydrocarbon receptor interacting protein).

### Clinical Presentation

Acromegaly is a rare disease, and the rate of change of symptoms and signs is slow and insidious. The usual period from earliest onset of symptoms and signs to diagnosis is 8 to 10 years, during which time many patients undergo medical and surical treatments for many of the metabolic abnormalities and morbidities caused by GH excess. Characteristic clinical findings of this disease include physical changes of the bone and soft tissue and with multiple endocrine and metabolic abnormalities (Table 62-4).

### Diagnosis and Differential Diagnosis

Measurement of serum IGF-I can be used to diagnose excess GH in most patients with acromegaly. An alternative is an oral glucose tolerance test using a 100-g glucose load. Normally, glucose suppresses GH levels to less than 1 ng/mL after 2 hours; in patients with acromegaly, GH levels may paradoxically increase, remain unchanged, or decrease but not below 1 ng/mL. Most acromegalic patients have GH-secreting pituitary tumors, and approximately 70% of cases of acromegaly are caused by pituitary macroadenomas. Rarely, GH hypersecretion is caused by ectopic GHRH-secreting tumors, including hypothalamic hamartomas and gangliocytomas, pancreatic islet cell tumors, small cell carcinoma of the lung, carcinoid, adrenal adenomas, and pheochromocytomas. Ectopic GH secretion has also been reported in pancreatic, lung, and breast cancers.

**TABLE 62-4 CLINICAL FEATURES OF ACROMEGALY**

| CHANGE | MANIFESTATIONS |
|---|---|
| **SOMATIC CHANGES** | |
| Acral changes | Enlarged hands and feet |
| Musculoskeletal changes | Arthralgias |
| | Prognathism |
| | Malocclusion |
| | Carpal tunnel syndrome |
| | Proximal myopathy |
| Skin changes | Sweating |
| Colon changes | Polyps |
| | Carcinoma |
| Cardiovascular symptoms | Cardiomegaly |
| | Hypertension |
| Visceromegaly | Tongue |
| | Thyroid |
| | Liver |
| **ENDOCRINE-METABOLIC CHANGES** | |
| Reproduction | Menstrual abnormalities |
| | Galactorrhea |
| | Decreased libido |
| Carbohydrate metabolism | Impaired glucose tolerance |
| | Diabetes mellitus |
| Lipids | Hypertriglyceridemia |

### Treatment and Prognosis

Treatment of acromegaly requires both treatment of the tumor and normalization of GH and IGF-I levels, along with management of the comorbidities and metabolic abnormalities caused by the excess GH. Treatment often requires the use of multiple modalities to achieve adequate control of the disease. Primary therapy is almost always transsphenoidal surgery, with the cure rate being directly proportional to tumor size. Patients with intrasellar microadenomas have a 75% to 95% cure rate with surgery. Even in patients with noninvasive macroadenomas, surgical removal results in normalization of IGF-I in 40% to 68% of patients.

Approximately 40% to 60% of tumors are not controlled with surgery alone because of cavernous sinus invasion or intracapsular intra-arachnoid invasion. Additional treatment options include primary medical therapy or primary surgical debulking of the tumor followed by medical therapy for hormonal control and/or radiation therapy for treatment of residual tumor. Conventional radiotherapy can normalize GH and IGF-I levels in more than 60% of patients, but the maximum response takes 10 to 15 years to achieve. Focused single-dose gamma knife radiotherapy has a 5-year remission rate of 29% to 60%. Hypopituitarism is seen in more than 50% of patients within 5 to 10 years after radiotherapy.

Currently, three drug classes are used to treat acromegaly: dopamine agonists, somatostatin receptor ligands (SRLs) such as octreotide and lanreotide, and GH receptor antagonists. SRLs work mainly through the somatostatin receptor subtypes 2 and 5, causing a decrease in tumor GH secretion. In acromegaly, SRLs are indicated for first-line treatment when there is low probability of surgical cure, after a failed surgical cure of GH hypersecretion, preoperatively to improve severe comorbidities that prevent or could complicate immediate surgery, and to provide GH and IGF-I control or partial control while waiting for radiotherapy to achieve its maximum effect. SRLs reduce GH and IGF-I levels to normal in 40% to 65% of patients and shrink tumor size in approximately 50% of cases. Side effects of SRLs include diarrhea, abdominal cramping, flatulence, and cholelithiasis (15%).

Pegvisomant is the only GH receptor antagonist available. It works by blocking the peripheral action of GH through blockade of the GH receptors located on the liver. Pegvisomant is indicated for patients who have persistent elevation in IGF-I even with maximum doses of SRLs. This drug is highly effective in the treatment of acromegaly and normalizes IGF-I levels in 97% of patients; transient elevation in liver function enzymes is seen in 25% of those treated, and tumor growth in fewer than 2%.

Cabergoline is the most efficacious of the dopamine agonists for treatment of acromegaly, but it is effective in fewer than 10% of patients.