Comprehensive Management of Acromegaly

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The somatostatin analog octreotide has a defined role in the overall management strategy for patients with acromegaly. Octreotide is effective in managing acromegaly both as an adjuvant to surgery and as a primary therapy. Octreotide is also beneficial to radiotherapy-treated patients in that the drug suppresses growth hormone (GH) secretion until the long-term ablative effects of radiation occur. Older patients, those with microadenomas, and those with systemic sequelae of hypersomatatropism benefit from initial primary medical therapy with octreotide. In these patients, the almost invariable biochemical normalization achieved by octreotide therapy renders it an effective alternative to surgery. Complications associated with octreotide are minor in comparison to the benefits, but the requirement for multiple daily injections is currently a major drawback. Approximately 25% of octreotide-treated acromegaly patients develop asymptomatic gallstones or sludge that require no treatment. The impact of sustained attenuation of GH and insulin-like growth factor-I (IGF-I) levels by octreotide on the pathogenesis of the long-term sequelae of hypersomatatropism can now be prospectively evaluated. Novel longer-acting octreotide-delivery mechanisms and new-generation somatostatin analogs will provide further advantages for primary pharmacotherapy in acromegaly.

ACROMEGALY is caused by growth hormone (GH) hypersecretion and resultant elevated circulating insulin-like growth factor-I (IGF-I) concentrations.[1] Management of acromegaly is directed at removing the lesion causing GH hypersecretion or at functional suppression of GH secretion.[2] Early intervention may prevent the irreversible skeletal changes and soft-tissue alterations associated with prolonged exposure to elevated GH levels, and may also result in a decrease of the enhanced mortality rates. Overall, therapy is thus directed toward normalizing biochemical parameters and ameliorating the systemic sequelae of hypersomatatropism, thus improving patient well-being and longevity.[3]

TREATMENT OF ACROMEGALY

Surgery

The primary treatment of acromegaly is surgical resection of GH-cell adenomas by the transsphenoidal approach.[4] Surgical resection of microadenomas is effective in over 70% of small circumscribed tumors. Macroadenomas have poorer prognoses following surgical resection, particularly when they exhibit extrasellar growth; such patients usually have persistent postoperative GH hypersecretion. Surgery relieves compression on adjacent structures such as the optic chiasm and ventricles. Local side effects of surgery include cerebrospinal fluid leakage and arachnoiditis; diabetes insipidus, which may be temporary or permanent; and permanent pituitary failure. These occur in approximately 20% of patients. Macroadenomas with extrasellar invasion are associated with intraoperative difficulties in identifying and removing tumor tissue. Recurrences also occur in some patients in whom surgery produced an initial remission, suggesting either continued adenoma growth or incomplete surgical resection with persistent tumoral hypersecretion. The age of the patient and general systemic health status will determine the relative contraindications for surgery as balanced against the potential advantages of surgery.[5]

Radiation

For patients who have persistent postoperative GH hypersecretion or who are poor surgical risks, radiation therapy may be effectively used.[6] The response of the tumor to radiation treatment is slow, requiring up to 5 years before a significant decrease in GH is achieved and up to 20 years for 90% of patients to achieve GH levels of less than 5 ng/mL. Improved precise isocentric simulators and accurate-delivery dosing techniques have resulted in improved complication rates. These rarely include optic nerve damage, cranial nerve palsies, impaired memory, lethargy in particular, and local tissue necrosis. Radiation damage to the surrounding normal pituitary invariably results in hypogonadism, hypocortisolism, or hypothyroidism in over half of all patients within 10 years. Gamma-knife radiosurgery is currently under investigation, and the results and long-term side effects of this novel therapy are presently unknown.

Octreotide

The pharmacology of this long-acting somatostatin analog is reviewed elsewhere in this symposium. Up to 90% of patients receiving octreotide exhibit suppressed GH levels, whereas over half achieve serum GH levels of less than 5 ng/mL, and about 70% normalize their IGF-I levels.[7-12] Octreotide provides a rapid and effective clinical response in the majority of patients. The drug acts rapidly, decreasing GH levels within 2 hours of administration, and a reduction in tumor size of up to 50% occurs in approximately half of all patients. Octreotide reduces debilitating headaches, improves joint pain, and ameliorates excessive perspiration, cardiac failure, and sleep apnea.[13-14] Importantly, intrinsic pituitary function remains intact in patients receiving the medication.

Side Effects of Octreotide Treatment

Abdominal pain, loose stools, mild fat malabsorption, nausea, and flatulence occur commonly on initiation of

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Table 1. Acromegaly Patient-Focused Management

- Patient self-image
- Arthralgias
- Cardiac failure
- Hypertension
- Diabetes
- Sleep apnea
- Side effects of therapy
- Interpretation of laboratory testing

treatment, and these side effects usually remit within 10 days even when treatment continues. In the long term, an increased incidence of cholesterol gallstone development occurs in up to 25% of patients.[15-17] Octreotide-induced gallstones are geographically variable and are determined by dietary, environmental, or hereditary factors. In China in particular, octreotide-induced gallstone formation is three times higher than that reported in the United States.[18] The overwhelming majority of octreotide-induced gallstones are asymptomatic and are only diagnosed by ultrasound, and in the long term only 1% of these asymptomatic individuals per year will be expected to develop symptoms. Octreotide-induced gallstones may disappear spontaneously in some patients, and those patients who do not develop echogenic gallbladder particles within the first 18 months of therapy probably will not ultimately develop gallstones.[19]

A COMPREHENSIVE STRATEGY IN THE MANAGEMENT OF ACROMEGALY

Overall, the management of acromegaly should be patient-focused, and as outlined in Table 1, treatment of systemic illness and achievement of patient well-being should be the overriding therapeutic goal.[19] Patient self-image should be an early focus of management. Psychological counseling and reconstructive facial and/or jaw surgery may be indicated. Systemic sequelae of acromegaly may require active intervention by a cardiologist, rheumatologist, or sleep specialist, in addition to the direct endocrine-metabolic management. The suggested management of GH-secreting microadenomas and macroadenomas is outlined in Figs 1 and 2. Naturally, individual patient variations in symptom severity, etiology of GH hypersecretion, age, and health status will determine the ultimate management choice.

Patients with microadenomas (< 10 mm and no extrasellar invasion) and mean plasma GH levels of less than 20 ng/mL should be offered, as informed choices, either surgery or octreotide treatment depending on their age. Full knowledge of the respective risks and benefits of each therapeutic modality can now be discussed with patients and used in attaining maximal and safe management. Elderly and/or asymptomatic patients may require no therapy, since there is little evidence that active therapeutic intervention will alter their life expectancy. When surgery is followed by persistent GH hypersecretion (as indicated by nonsuppressible GH and elevated IGF-I levels,[20,21] either octreotide or irradiation should be initiated even in asymptomatic patients. If radiation is selected as an adjunctive postoperative therapy, octreotide is required to control symptoms and prevent further deleterious effects of hypersomatotropism until radiation treatment takes effect (perhaps up to 15 or more years).

In patients with macroadenomas with extrasellar tumor extension and mean GH levels usually less than 20 ng/mL (Fig 2) therapy is not indicated in elderly patients with other debilitating systemic illness or in the absence of their exhibiting acromegaly-associated morbidity. Because of the risks of surgery in elderly acromegalic patients and the prolonged period needed for radiation to be effective, octreotide is indicated. Whether preoperative octreotide improves subsequent postsurgical cure rates is currently unclear, and this question requires controlled prospective data.[22]

Transsphenoidal surgery is the best primary therapeutic

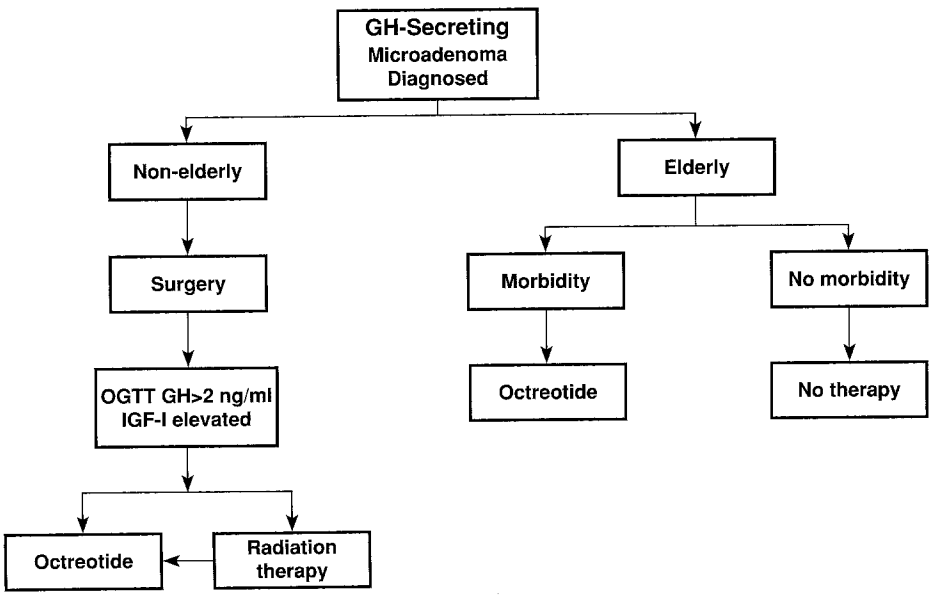

Fig 1. Paradigm for the management of acromegaly caused by pituitary microadenoma (<10 mm in diameter) and serum GH levels of less than 20 ng/mL. OGTT, oral glucose tolerance test. (Adapted from reference 19.)

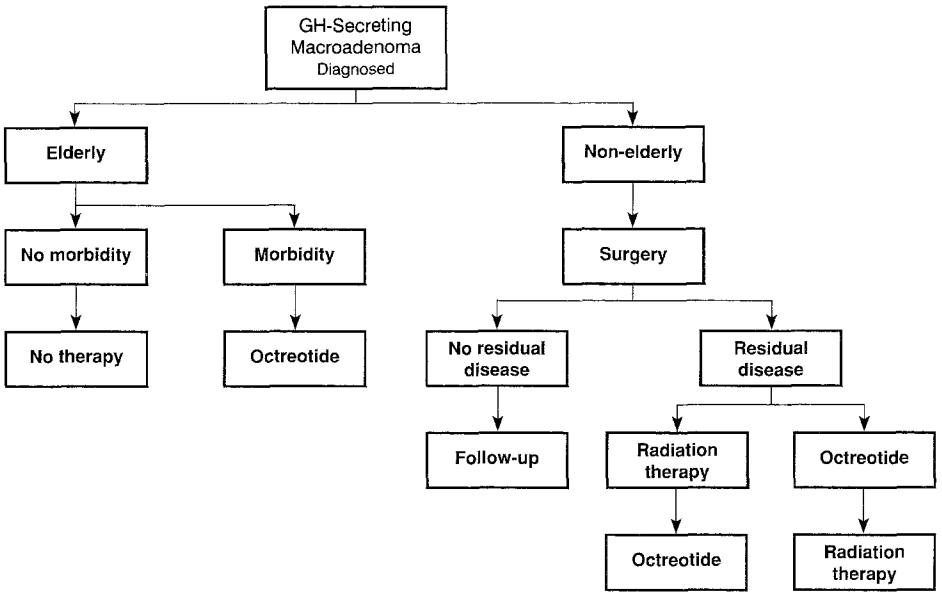

Fig 2. Paradigm for the management of aoromegaly caused by macroadenoma (>10 mm in diameter) and GH levels >20 ng/mL. OGTT, oral glucose tolerance test. (Adapted from reference 19.)

choice in young patients with acromegaly. If GH/IGF-I are normalized after surgery, no additional therapy is usually required. If surgery fails to normalize GH, adjunctive radiation or octreotide is indicated. Radiation will not normalize GH initially and acromegalic symptoms will persist, requiring alternative treatment with octreotide. The analog is therefore the most efficacious and safest fall-back therapy for persistent GH hypersecretion or recurrent disease after surgery or radiation.[23]

Ultimately, the effectiveness of octreotide depends on the somatostatin receptor status of the GH-cell adenoma.[24] Modern molecular techniques are now being applied to determine pituitary tumor receptor subtypes, and these will surely result in novel therapeutic agent development.[25] In the future, improved delivery methods (including long-acting formulations) and second-generation drugs (including new analogs) will provide further advantages in the pharmacotherapy for pituitary tumors.

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