Acromegaly

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Subcellular mechanisms support the notion of an intrinsic pituitary defect in acromegaly, with elevated growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels that affect the cardiovascular and respiratory system, as well as neoplastic cell proliferative activity. Surgery, even with external-beam irradiation adjuvant therapy, is only successful in less than 60% of patients, and there are side effects. Normalization of GH levels may improve survival rates. Octreotide has revolutionized patient management, normalizing GH and IGF-1 levels in up to 60%, ameliorating soft-tissue abnormalities and reducing tumor size in up to 50%, and attenuating GH levels in more than 90% of patients. Issues concerning the role of octreotide, as well as clarifying precise outcome measures, still need to be resolved.

RECENT ADVANCES in acromegaly[1] include novel insights into disease pathogenesis, impact of elevated growth hormone (GH) and insulin-like growth factor-1 (IGF-1) on morbidity and mortality, and novel therapeutic options.

PATHOGENESIS

For several years, both hypothalamic and pituitary etiologies were implicated in the pathogenesis of acromegaly. Since the recent observation that GH-cell adenomas are monoclonal, several subcellular mechanisms have been elucidated that support the notion of an intrinsic pituitary defect in acromegaly. These include loss of heterozygosity of chromosomal DNA (putative tumor-suppressor gene), defects of intrapituitary signal transduction, disordered transcriptional regulation, genetic markers of tumor invasiveness, and characterization of hypothalamic receptors on the somatotroph cell. Finally, hypothalamic disorders, including aberrant GH-releasing hormone (GHRH) secretion, are being further unraveled.

IMPACT OF EXCESSIVE GH ON MORBIDITY AND MORTALITY

The most significant deleterious effects of elevated GH and IGF-1 levels include those on the cardiovascular and respiratory system, as well as on neoplastic cell proliferative activity. Cardiovascular side effects of acromegaly occur in at least one third of patients and include hypertension, left ventricular hypertrophy, atherosclerosis, left ventricular diastolic overload, and assorted arrhythmias. It is as yet unclear whether GH contributes directly to a specific cardiomyopathy or whether the cardiac changes are secondary to vessel wall thickening, hypertension, and fluid retention. Although cardiomegaly often regresses in concert with lowering GH levels, hypertension usually persists, regardless of GH levels attained by therapy. Respiratory side effects include both obstructive and central sleep apnea with accompanying elevated P_{CO_2} levels and resultant complications of respiratory function.

The impact of GH and IGF-1 on malignancy has recently been intensely studied. Several in vivo and in vitro lines of evidence point to a permissive role for the GH–IGF-1 axis on tumor proliferation. In vitro evidence and limited retrospective clinical data have implicated GH in cell transformation and proliferation, especially in the colon. No direct proof has been shown that GH itself initiates a spontaneously occurring human tumor. However, IGF-1, as well as its ligand-activated receptor, has been shown to induce cell transformation in several in vitro and animal models.

RATIONALE FOR NORMALIZING GH LEVELS IN ACROMEGALY

Several factors have been shown to directly impact mortality and morbidity in acromegaly. These include the GH concentration attained and duration of disease, ie, length of time of exposure to abnormally elevated GH levels. Clearly, preexistent cardiovascular disease or diabetes present before the diagnosis of acromegaly has a severe impact on mortality. Several retrospective studies now demonstrate that normalization of GH levels may actually result in a favorable reversal of adverse mortality rates. A clear rationale is therefore now evident for suppressing GH and IGF-1 levels as effectively as possible.

THERAPY

Surgery has been a mainstay of therapy ever since Cushing's first successful, trans-sphenoidal resection for acromegaly in 1910. Although more than 70% of small circumscribed GH-cell adenomas are successfully cured in experienced surgery centers, most patients present with larger tumors. Persistent GH hypersecretion or surgically inaccessible tumor invasiveness occurs in the majority of these patients. External-beam irradiation has been utilized as adjuvant therapy. Each of these therapeutic modalities only provides a successful outcome in less than 60% of all patients, and each also has unique side effects.[2]

The recent advent of peptidomergic therapy has revolutionized the approach to managing these patients. Octreotide effectively normalizes GH and IGF-1 levels in up to 60% of patients, and ameliorates soft-tissue abnormalities and reduces tumor size in up to half of all patients. GH levels are actually attenuated in more than 90% of patients,

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presumably reflecting the presence of tumor somatostatin receptors.[3,4]

Although the favorable experience with octreotide has benefitted patients who have failed to respond to surgery, or those who have foregone surgery or irradiation, several important unanswered questions remain. These include the following:

(1) What are "normalization" criteria for GH in the treated adult population? In the absence of a definitive answer to this question, absolute criteria of therapeutic success cannot be determined.

(2) What are the long-term side effects of octreotide?[3] Although geographic-dependent asymptomatic gallstones appear to be the most important side effects, additional long-term effects, although unlikely, are still possible.

(3) When will a long-acting somatostatin analog become available? Clearly, one of the most important drawbacks to octreotide therapy is the requirement for every-8-hour subcutaneous injections. The availability of a long-acting compound will certainly be a major determinant of therapeutic choice for endocrinologists and their patients.

(4) What advances can we expect from development of novel stereotactic and radiosurgical techniques, and how will these impact our approach to therapy?

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