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Treatment of Acromegaly

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Abstract:

Acromegaly is a chronic debilitating disorder resulting from excessive secretion of growth hormone and a resulting increase in the production of insulin-like growth factor I (IGF-I). It is usually caused by somatotroph adenomas of the pituitary gland. The goal of treatment is to reverse the effects of the hyper-secretion of growth hormone and normalize production of IGF-I. Effective treatment ameliorates the symptoms and signs of the disease and lowers the mortality rate.

Introduction:

Acromegaly is a hormonal disorder that results from excessive secretion of growth hormone (GH) in the body. The pituitary, a small gland in the brain, makes GH. Usually the excess GH comes from benign, or noncancerous tumors on the pituitary. These benign tumors are called adenomas. (1)

Acromegaly is most often diagnosed in middle-aged adults, although symptoms can appear at any age. If not treated, acromegaly can result in serious illness and premature death. Acromegaly is treatable in most patients, but because of its slow and often "sneaky" onset, it often is not diagnosed early or correctly. (2) The most serious health consequences of acromegaly are type 2 diabetes, high blood pressure, increased risk of cardiovascular disease, and arthritis. Patients with acromegaly are also at increased risk of colon polyps, which may develop into colon cancer if not removed.

Unfortunately, no single therapy is comprehensively successful in controlling the disease and its protean clinical manifestations, and different treatment modes are associated with unique adverse effects and clinical disadvantages(3). Small pituitary adenomas are common, affecting about 17 percent of the population. However, research suggests most of these tumors do not cause symptoms and rarely produce excess GH. Scientists estimate that three to four out of every million people develop acromegaly each year and about 60 out of every million people suffer from the disease at any time. (1) Because the clinical diagnosis of acromegaly is often missed, these numbers probably underestimate the frequency of the disease.

Surgery, radiation, and medical treatments are available for lowering GH and IGF-I hyper-secretion, controlling pituitary tumor mass effects, and improving morbidity.

Recent studies provide a compelling rationale for controlling GH and IGF-I secretion as being the most significant determinant of restoring the observed adverse mortality to control rates. [4–6] Regardless of the therapeutic mode, the goal of treatment is to control GH levels to less than 1 μg/liter after an oral glucose load ,normalize age- and gender-matched IGF-I levels, ablate or reduce tumor mass preventing its recurrence, and alleviate significant comorbid features, especially cardiovascular, pulmonary, and metabolic derangements.

The aim of this report is to illustrate the advantages and disadvantages of different types of therapies used to treat acromegaly.

Materials and Methods:

The first line of therapy that should be used for the acromegalic patient is transsphenoidal surgery especially if a micro-adenoma (<1 cm) or small macro-adenoma without invasion of the cavernous sinus is present. If GH levels during OGTT are greater than 2 ng/mL, the IGF-I level is elevated, or there is tumor persistence after surgery, other lines of medical therapy should be initiated and they include (soatostatins, dopamine agonist and GH receptor antagonist). Although radiation therapy may also be considered by some, because of the many disadvantages that can be caused by radiation therapy, it is recommended only if medical treatment fails.

Results:

Therapy allows serum IGF-I concentrations to be normalized in up to 92% of patients with acromegaly.

Discussion:

The goals of treatment are to reduce GH production to normal levels, to relieve the pressure that the growing pituitary tumor exerts on the surrounding brain areas, to preserve normal pituitary function, and to reverse or ameliorate the symptoms of acromegaly.

The likelihood of surgical cure by experienced neurosurgeons in such cases is 70% or greater, an immediate outcome after surgery should result in GH levels less than 2 ng/mL (OGTT) and a normalized IGF-I level. These patients should be evaluated 6 weeks post-surgery with measurement of GH and IGF-I levels. MRI may be performed at 3 months if the values have not normalized. Sometimes, IGF-I levels remain elevated post-surgery despite normalization of GH. The decision to treat or monitor these patients is based on clinical criteria of disease activity.

For patients with minimally elevated GH levels post-surgery, octreotide or dopamine agonist therapy may be appropriate, and the selection should be made based on expected efficacy and factors such as cost, patient quality of life, and compliance. Nonsurgical treatment options for acromegaly include medical therapy with somatostatin analogs or dopamine agonists and radiotherapy .These therapies have been most effective when used in conjunction with surgery in the appropriate clinical context, however these medications come with a set of adverse effects that should be considered before initiating the treatment. Somatostatin is an endogenous molecule that exerts a variety of physiological effects, including inhibition of GH secretion. Due to the short half-life of native somatostatin, longer acting and selective somatostatin analogs (i.e. octreotide, lanreotide, vapreotide) have been used to treat acromegaly, in recent long-term studies, GH levels were suppressed to less than 5 ng/mL in 65% of patients and to less than 2 ng/mL in 40% of patients. Importantly, octreotide was shown to normalize IGF-I levels in approximately 60% of patients. in a study by Newman et al., 56 of 87 treated patients (64%) achieved normal IGF-I levels. Tumor shrinkage occurs with octreotide, but it is generally modest. The primary side-effect associated with octreotide therapy is increased risk of asymptomatic cholesterol gallstone development, which occurs in up to 25% of patients.

Short term side-effects that often resolve with continued treatment include abdominal pain, diarrhea, fat malabsorption, nausea, and flatulence. Clinically insignificant bradycardia occurs in approximately 25% of patients .For those who are unresponsive to somatostatin analogues, or for whom they are otherwise contraindicated it is possible to treat using one of the dopamine agonists, bromocriptine or cabergoline.

Dopamine agonists bind to pituitary dopamine type 2 (D_2) receptors and suppress GH secretion in some patients with acromegaly, although the precise mechanism of action remains unclear. Historically, bromocriptine provided subjective symptom relief for patients before the availability of other pharmacological treatments, Side-effects associated with this treatment include nausea, vomiting, abdominal spasm, nasal stuffiness, arrhythmia, effects on the central nervous system, sleep disturbances, fatigue, transient postural hypotension, and cold-induced peripheral vasospasm (ergotism)[4].

Radiation therapy is usually reserved for patients who have tumor remaining after surgery. Both conventional and heavy particle (proton beam) irradiation have been used to treat acromegaly. The beneficial effects of radiotherapy on GH levels are dose dependent and delayed. It is not until up to 20 yrs. after therapy that 90% of patients have GH levels less than 5 ng/mL. Furthermore, results from a number of pivotal studies from major radiotherapy treatment centers have shown that approximately 50% of patients achieve adequate GH suppression within 10 yrs. after radiation, During the interim between treatment and optimal GH reduction, patients may require adjunctive medical therapy[5]. Several factors may render radiotherapy ineffective in treating acromegaly.

Recently a study reported the ineffectiveness of radiotherapy in lowering IGF-I levels despite the attenuation of GH levels. Cranial radiotherapy frequently results in abnormal hypothalamic-pituitary function, including hypothyroidism and gonadal dysfunction, which require target hormone replacement. Rarely, other adverse effects, such as visual disturbances (including blindness), the development of a secondary brain malignancy, brain necrosis, and brain damage, have been reported. [6]

Conclusion:

The treatment approach presented here is designed to address the appropriate use of various therapies for acromegaly. It is important to note that the treatment has advantages and disadvantages. Although these therapies have proved effective in treating acromegaly, they have their disadvantages. for example, somatostatin might have a rapid onset with no hypopituitarism; however the multiple injections used to get the drug into the circulation as well as the cost of the drug might pose a problem for some patients. The same goes for dopamine agonists in addition they require high doses to be effective. As for radiotherapy, the advantages could be that it's a one-time cost and doesn't require multiple sessions; however the side effects could be very dangerous as it can lead to visual problems and possible brain damage. In conclusion, no single treatment is effective for all patients, treatment should be individualized, and often combined, depending on patient characteristics such as age, and tumor size.

Future work:

The need for new therapeutic agents and modalities for patients with acromegaly.

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