A Case-Based Guide to Clinical Endocrinology

Second Edition

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Editor

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Preface

Where I come from in the North of England, a “second” refers to a piece of china with a fault in the decoration or a chip before entering the furnace. Buying “seconds” of very expensive china at low prices was, and is, a common practice of my middle class upbringing. So the term “second edition” does not do this volume justice in my own mind and it is unlikely to be gotten at a rock bottom price. I prefer to call it another volume. Of course there are a few reasons for another volume of Endocrinology Case Histories, but the most obvious is the fact that the earlier volume has created a demand. There was, at least to me, a surprisingly warm reception to the earlier case histories, and this was particularly evident in the download history. People still read a few paper books but the number reading digital versions is clearly exploding. One reason is the easy availability on an international scale. Another is that case histories are perfect for short commutes and the need for a quick revision. And let’s not forget that the quality matters also. Having able and dedicated authors willing to submit their teaching cases and then holding their patience during the still long production period is the essential component of this book. I thank them all; many doing this a second time. The demands on medical practitioners continue to increase with no sign of relief and so our free time has become less and less and so has the willingness of many to contribute to such collections. This is a great shame because the multiplicity of authors makes for splendid reading; you never know what style is next and how the case will be revealed. I want to thank the Springer team, especially Richard Lansing and Maria Smilios, for encouraging the production of this collection. There is a lot of good and modern medicine to be learned here.

New York, NY, USA — Terry F. Davies

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Part XII Obesity

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Part I
Pituitary

Chapter 1
Introduction

Maria Fleseriu

Secretory Pituitary Adenomas

Pituitary adenomas can cause symptoms by hormonal hypersecretion. Hypersecretion of prolactin (PRL) is responsible for amenorrhea–galactorrhea in women and decreased libido in men, growth hormone (GH) for acromegaly, adrenocorticotropic hormone (ACTH) for Cushing's disease, and thyroid-stimulating hormone (TSH) for hyperthyroidism. Tumor mass-related effects such as headaches, visual field abnormalities, and depression of hormonal secretion (hypopituitarism) may also be present.

All patients who present with a pituitary tumor should be evaluated for gonadal, thyroid, and adrenal function as well as an assessment of PRL and GH. To detect the cause of hypersecretion and response to treatment, specific pituitary hormone stimulation and suppression tests are performed, in selected cases. To determine the presence, size and extent of the lesion magnetic resonance (MR) imaging (unless contraindicated) is the gold standard.

Pituitary tumor classification is based on cell cytoplasm staining properties as viewed by light microscopy and immunocytochemistry. Silent functioning adenomas (clinically nonfunctioning adenomas) also exhibit positive pituitary cell-type immunostaining. Most commonly, these include silent gonadotroph adenomas, silent corticotroph adenomas, and silent somatotroph adenomas.

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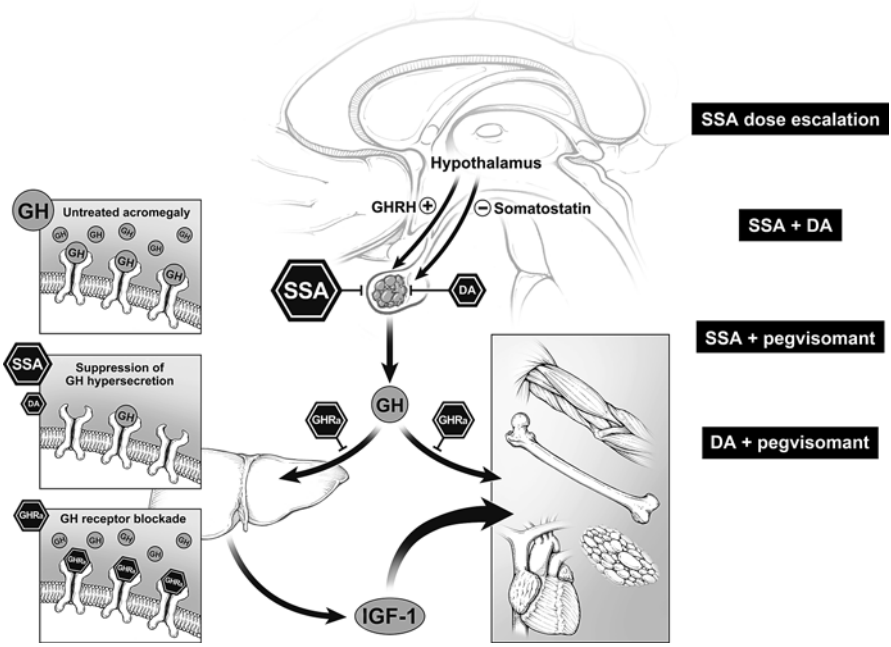

Fig. 1.1 Adapted from *Neurosurg Focus* 29(4):E15, Fleseriu, M., Delashaw, J.B., and Cook, D.M. *Acromegaly: a review of current medical therapy and new drugs on the horizon,* page 3, Copyright (2010), with permission from Journal of Neurosurgery Publishing Group and American Association of Neurological Surgeons

In the last few decades, significant improvement in surgical technique (>99 % of cases performed via a transphenoidal route) has resulted in low mortality rates. Medical treatment with therapeutics such as dopamine agonists (DA), somatostatin analogs (SSA), GH-receptor antagonists, and glucocorticoid receptor (GR) antagonists has had a profound impact on the indications for radiotherapy. Generally, drugs are now utilized as a second-line treatment, (after surgery) or even as a first-line treatment (Fig. 1.1). Radiotherapy, in selected cases, using stereotactic techniques such as gamma-knife, has been relegated to a third-line treatment. Recently, temozolomide, an orally active alkylating agent used principally in the management of glioblastomas, was shown to be effective in controlling aggressive/invasive pituitary adenomas/carcinomas.

Pituitary tumor patients are best cared for by a multidisciplinary neuroendocrine team at a specialized center; one that includes neurosurgeons, endocrinologists, radiation oncologists, neuro-ophthalmologists, and otolaryngologists. No single treatment algorithm applies to all patients. Treatment should be individualized and include long-term follow-up. Treatment models for individual pituitary adenomas vary and are summarized above (Fig. 1.1).

Prolactinomas

Prolactinomas are the most common type of hormone-secreting pituitary tumor. First-line therapy is with DAs. Surgery is generally reserved for patients who do not respond to medical therapy, with severe pituitary hemorrhage, are pregnant with progressive tumor enlargement or are not responding to DA therapy.

Treatment aims to normalize PRL levels, restore fertility in those of child-bearing age, decrease tumor mass, save or improve the residual pituitary function, and inhibit disease relapse. Dopamine agonists available in the United States (US) are bromocriptine and cabergoline.

Cabergoline is usually better tolerated (less headache, nausea, postural hypotension, and fatigue) and offers the convenience of twice-a-week administration; starting dose is usually 0.25 mg up to a maximum dose of 1 mg. Cabergoline appears to be more effective in lowering PRL levels within the first 2–3 weeks of treatment in about 90 % of patients and in restoring ovulation. The drug usually decreases the size of micro- and macroadenomas (several weeks to months to observe detectable decreases). In cases whereby the adenoma affects vision, improvement may be observed within days of starting treatment. If tumor response to drug is therapeutically good, medical therapy can be withdrawn after 3–5 years. Hyperprolactinemia will not recur in two-thirds of these patients.

The best treatment to restore fertility in women with a microadenoma is a DA. Cabergoline is less used in women attempting conception or in pregnancy. Bromocriptine does not appear to increase the risk of miscarriage or birth defects when discontinued early in pregnancy. Before attempting pregnancy, a detailed discussion with patients should include when to discontinue bromocriptine, the chances that the adenoma will grow during pregnancy and further treatment details as necessary. Microadenomas rarely increase in size during pregnancy. On the other hand, if the adenoma is large or is affecting vision, surgery is usually recommended before attempting to conceive.

Acromegaly

Treatment of GH-secreting adenomas should include a comprehensive treatment strategy to alleviate pituitary tumor effects, normalize GH and insulin-like growth factor-1 (IGF-1) hypersecretion, improve associated comorbidities, and reverse the increase in mortality risk, all while preserving normal pituitary function. Surgery is the first-line treatment choice for acromegaly patients, with two caveats, an experienced surgeon is available and tumor is visible on MR imaging. If the tumor has invaded the cavernous sinus, or has been determined to be not completely resectable, medical therapy can be also offered as first-line treatment in addition to surgery. The treatment of patients with persistently active acromegaly has been facilitated over the past decade by the advent of highly specific and selective pharmacological agents that are sometimes used in combination. Radiation

therapy is a potential adjuvant therapy, usually reserved for patients who have some remaining tumor postsurgery. These patients often concomitantly take medications to lower GH levels as there is usually a long waiting period before radiation is effective. Decrease in pituitary function (hypopituitarism) is a significant complication. Radiotherapy remains a third-line treatment option for acromegaly in the US.

Three classes of medical therapy are available to treat acromegaly, each with unique advantages and disadvantages. In patients with uncontrolled hormone levels after surgery, SSAs are the first-line treatment choice. Dopamine agonists and GH receptor antagonists are generally indicated after failure of SSAs or in combination with SSAs (Fig. 1.1).

Somatostatin Analogues

There are three SSAs approved for use in the US: octreotide short release, octreotide long acting release (LAR) or Sandostatin LAR, and lanreotide ATG (Somatuline depot). It is difficult to appreciate the true efficacy of SSAs in achieving biochemical control due to varied clinical trial study entry criteria and "desirable" cut-off goals. Although early on a study data meta-analysis showed that overall GH and IGF-1 were normalized in 49–56 % and 48–66 % of patients, respectively. Other study results suggest symptom control in a large majority, with biochemical control only being achieved in approximately half of patients if "unselected" for responsiveness. Somatostatin analogues are generally safe and well tolerated. The most frequent adverse events of SSA treatment are abdominal symptoms, which usually improve over time glucose intolerance and gallbladder sludge/stones. The distinctions between different types of GH-secreting tumors (sparsely vs. densely granulated tumors), and presence of somatostatin receptor type 2a (SSTR2a) can impact response to therapy as well as prognosis; therefore, accurate classification is important.

It has been suggested that SSA treatment prior to surgery can reduce surgical risks and potentially improve surgical cure rates. Conversely, tumor debulking is often used with SSA therapy when GH is partially but not completely controlled with treatment. In these cases, debulking the tumor may allow SSA therapy to reduce GH and IGF-1 into the normal age-adjusted range.

A number of studies have reported tumor shrinkage in patients with acromegaly treated with SSA therapy, both adjunctive and primary. This shrinkage can be significant (20–80 % in about one-third of patients), however results are unpredictable.

Dopamine Agonists

Dopamine agonists inhibit GH secretion in some acromegaly patients. The beneficial effects could occur even when pretreatment PRL levels are normal and/or there is no evidence of tumor PRL staining. A lower IGF-1 level at the start of

treatment seems overall to be the best predictor of efficacy. Cabergoline is administered orally and is thus more convenient, although not as effective as other medical therapies.

Growth Hormone Receptor Antagonists

The GH receptor antagonist, pegvisomant, (Somavert) directly inhibits the peripheral action of GH by interfering with functional dimerization of the two GH receptors subunits and thus blocks the signal for IGF-1 production. In early clinical trials, normalized IGF-1 levels were observed in approximately 90 % of patients, however, data from large observational studies has revealed a much lower IGF-1 normalization rate (70 % of patients), most probably due to inadequate dosage. Pegvisomant adverse events include disturbed liver function tests and injection site reactions. Tumor growth has not been proven to be a concern, but continued long-term surveillance of tumor volume is needed, especially in nonirradiated patients. It is recommended that pegvisomant be reserved for SSA nonresponders or patients intolerant of SSAs, patients whose diabetes is worsened by SSAs or considered in combination therapy.

For acromegaly patients who are poorly or non-responsive to, presently available single drug therapies, the use of combination drug therapy holds promise. However, currently the use of combination therapy is not approved by the Federal Drug Administration (FDA) in the US.

Monitoring Therapy

General consensus is to lower the IGF-1 levels to within the reference range for the patient's age and gender and to lower the random serum GH levels to <1 ng/mL or <0.4 ng/mL (depending on the assay) after a glucose load (oral glucose tolerance test; OGTT). Pegvisomant is unique in that the drug does not lower GH levels (levels are raised, due to feed-back mechanics), thus making IGF-1 the only available marker for disease activity.

It is recommended that all patients undergo biochemical testing and pituitary MR imaging during long-term follow-up, irrespective of medical treatment.

Drugs in Clinical Trial

The role of SSTRs and dopamine receptors (DR) as molecular targets for the treatment of pituitary adenomas is well established.

Pasireotide (SOM 230; Signifor) is a unique somatotropin release-inhibiting factor with a high binding affinity to SSTR subtypes 1, 2, 3, and 5 and up to a 40-fold greater affinity for $SSTR_5$ than octreotide. Phase III clinical trials results show that subjects treated with pasireotide LAR were significantly more likely to achieve disease control than those treated with octreotide LAR. Also, approximately 20 % of

subjects uncontrolled on octreotide achieved full disease control after switching to pasireotide LAR. However, a higher degree and frequency of hyperglycemia has been observed and reported with pasireotide use. The long-term and future role of pasireotide in treating acromegaly remains to be determined.

Alternate drug delivery systems are an exciting and developing area of research. Octreolin, an investigational oral form of octreotide, is currently being studied in a pivotal phase III clinical trial to determine efficacy and safety in acromegaly patients who are currently receiving parenteral SSAs.

Cushing's Disease

Cushing's disease (CD) is defined as hypercortisolism caused by an ACTH-secreting pituitary adenoma. While rare, the disease is associated with significant morbidity and mortality.

Treatment goals include the reversal of clinical features, normalization of cortisol levels, minimal morbidity, preservation of pituitary function, and long-term disease control without recurrence. In patients with macroadenomas, removal of the tumor mass is an additional treatment goal.

For most CD patients, primary treatment is transsphenoidal surgery to remove the pituitary adenoma. However, success rates are variable (reportedly, 65–90 % dependent on the surgeon's expertise) and recurrence rates are observed in more than 25 % of patients during long-term follow-up. Second-line therapy includes more radical surgery, radiation therapy (stereotactic radiosurgery), medical therapy, and lastly bilateral adrenalectomy.

While there are several potential CD therapeutic targets, clinical experience is lacking. Recently, however, prospective studies have demonstrated the potential of pituitary-directed medical interventions that target the underlying adenoma and block GRs. Medical therapies for CD patients are summarized below (Fig. 1.2).

Pituitary-Targeted Therapy

Corticotroph adenomas frequently express both dopamine (D2) and somatostatin receptors (predominantly $SSTR_5$). Pituitary-targeted therapies may provide both antisecretory and an antiproliferative treatment results. Research into patterns of receptor expression in corticotroph adenomas may lead to increased understanding of tumor pathogenesis, and allow development of therapies specifically tailored to individual patients following surgical pathology analysis.