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Management options for persistent functional tumors

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Unfortunately, it is common to discover that there is still evidence of endocrine overactivity after initial treatment of a functional pituitary adenoma. The endocrine assessment of the patient must be done meticulously and in a timely fashion. For example, in an acromegalic patient, the insulin-like growth factor type 1 (IGF-1) may remain elevated for several days or weeks after surgery and then fall into the normal range. The first task is to define exactly what is ''persistent function'' in a secretory tumor and then to decide how aggressively to treat the persistently high hormone levels. Persistence of elevated corticotropin and cortisol levels in a Cushing's disease patient is much more devastating than elevated prolactin levels in a patient with a prolactinoma. Because each type of functional tumor varies as to the definition of remission and the treatment options available for persistent function, each tumor is discussed separately.

Acromegaly

Definition of persistent function

For many years, successful remission after surgery was defined as a ''normal'' growth hormone (GH) of usually less than 5 ng/mL. It is now known that many patients with active acromegaly have a GH well below the level of 5 ng/mL. In our series of acromegalic patients, we found that even if the GH was below 1.5 ng/mL, the IGF-1 was elevated in 43% of patients (up to 320% of normal). Even though a substantial drop in GH allows significant improvement in clinical symptoms after surgery, the patient is considered to have persistence of tumor activity if the IGF-1 remains elevated. Nonsuppressibility of GH to below 1 ng/mL (or below 0.2 ng/mL using more sensitive assays and stricter criteria) is additional evidence of persistent GH autonomy. Which parameter (high IGF-1 or nonsuppressibility of GH) is a better reflection of persistent function of the tumor is still not clearly understood [1]. Because most, if not all, clinical manifestations of acromegaly result from high IGF-1, this parameter seems to be a better reflection of clinically important disease. Nonsuppressibility of plasma GH by glucose may indicate abnormal GH regulation that may or may not be of practical significance from a clinical point of view. Ideally, both parameters should be normalized [1], but whereas high IGF-1 requires some action, nonsuppressible GH per se may just be followed as a possible predictor of future recurrence.

Surgical options

If surgery by an experienced pituitary neurosurgeon has not resulted in endocrinologic remission, further surgery is rarely helpful. Unfortunately, the

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great majority of GH-secreting tumors are macroadenomas that are invasive of the surrounding structures [2]. If the preoperative imaging demonstrates invasion into the cavernous sinus, particularly lateral to the internal carotid artery, remission from surgery alone is not feasible. If the tumor is greater than 10 mm but has a well-defined border at the medial edge of the cavernous sinus, aggressive resection may well result in normalization of IGF-1. The ideal situation is a tumor less than 10 mm that is more centrally located within the gland. If this type of microadenoma is resected without remission, a more aggressive resection, including a complete hypophysectomy, may be contemplated, but the possibility of ectopic GH-releasing hormone (GHRH) secretion by a carcinoid or islet cell tumor also needs to be considered.

Medical options

Medical treatment of persistently elevated GH and IGF-1 levels after surgical resection has become an increasingly attractive alternative to external beam radiation. Currently, the most commonly used agents are the somatostatin analogues, octreotide, and lanreotide. These act by reducing the production of GH and must be given by injection. Octreotide acetate is manufactured in two galenic forms: a short-acting form for subcutaneous (SC) injection and long-acting Sandostatin LAR for monthly intramuscular (IM) injection. Lanreotide is currently approved in Europe but is not yet approved in the United States. A shorter acting preparation of lanreotide, Somatulin, is given every 7 to 14 days by IM injection, and a longer acting form (not yet approved), Autogel, is designed for deep SC injection monthly. The differences between these four preparations reflect mainly their relative potency, duration of effectiveness, convenience of administration, and local reimbursement policies. Each medication needs to be individually titrated to achieve normalization of plasma IGF-1 (1–2 weeks for SC octreotide, 1–2 months for either of the lanreotide preparations, and 3–4 months for Sandostatin LAR). All these medications are capable of normalizing IGF-1 in 50% to 70% of patients and of effecting clinically significant tumor shrinkage in 25% to 50% of patients. Side effects include bloating and biliary sludging or stone formation [3–5]. Somatostatin analogues can be used as primary therapy for acromegaly, especially in patients who have medical contraindications for surgery or whose tumors are so large and invasive that surgery would not be curative or even helpful in lowering GH levels. If a high percentage of an invasive unresectable tumor can be removed, this significantly lowers GH and improves the success rate of subsequent pharmacologic therapy.

Dopamine agonists such as bromocriptine, pergolide, or cabergoline reduce the GH in acromegalic patients but only rarely bring elevated GH and IGF-1 levels to normal [6]. These may be tried if a patient cannot tolerate the somatostatin analogues. Dosages for these medications are discussed in the section on prolactinomas.

Pegvisomant is a drug that is not yet approved for general use but seems promising in clinical trials. This is a GH receptor antagonist that has an increased affinity to binding site 1 and inactivates binding site 2, thus blocking the GH receptor and eliminating the adverse effects of elevated circulating GH [7].

Radiation options

Conventional radiation has been the mainstay of adjuvant therapy after unsuccessful surgery in the treatment of acromegaly. A standard dose of fractionated external beam radiation encompassing the entire residual tumor provides a 50% reduction in GH over 2 years. Because this is a slow ongoing reduction over a decade or more, it is critical that the initial postoperative preradiation GH level be as low as possible. There are many studies reporting the reduction of GH to less than 5 ng/mL with conventional radiation, but only recent studies report the postradiation levels of IGF-1. We looked at 38 patients with persistent GH activity after surgery at an average of 6.8 years after radiation, and only 2 patients had a normal IGF-1 level [8]. The remaining patients had persistently elevated IGF-1 levels ($219 \pm 26\%$ of upper normal limit), despite plasma GH levels averaging 4.6 ± 1.1 μg/L. Other authors have reported a higher percentage of success in normalizing IGF-1. Looking at all the available series, it seems that the IGF-1 can be normalized with conventional radiation in about 36% of patients [9]. Modern focused image-guided fractionated radiation is quite precise and allows little radiation to penetrate surrounding brain tissue. Although the optic pathways may be included in these fields, the dosage is such that there is little risk to vision.

Beginning 30 years ago, single-dose treatment with proton beam heavy particle therapy was used by Kliman et al [10] in 510 patients, 428 of whom

have been followed for between 1 and 20 years. Analysis of these patients reveals that there was a progressive decline in GH level beginning immediately after treatment and continuing for up to 20 years. At 2 years, 47.5% of patients had a GH less than 10 ng/mL, and at 4, 10, and 20 years, the rates were 65%, 87.5%, and 97.5%, respectively. A GH level of less than 5 ng/mL was achieved in 75% of patients at 10 years and in 92.5% of patients at 20 years. The only available direct comparison study between conventional external and stereotactic proton beam modalities failed to detect any difference in efficacy at 5 years [11].

Stereotactically guided single high-dose radiation, so-called "radiosurgery," has been available at selected centers for more than 20 years. Recently, the gamma knife and various LINAC systems have become widely available and increasingly used to treat residual GH-secreting tumors. Although experience with this type of radiation is more limited, it seems that the overall normalization of IGF-1 is similar to that with conventional radiation, although perhaps slightly faster. Review of current reported experience suggests an overall normalization of IGF-1 of about 33% [9]. The ability of any radiation modality to arrest tumor growth, and even to shrink tumors, is an important advantage of radiotherapy. Thus, although pharmacologic modalities have largely replaced radiation as the first choice for adjuvant therapy, radiation is still the treatment of choice for a minority of patients whose tumor remnants do not shrink (or even grow) despite somatostatin analogue therapy.

Cushing's disease

Definition of persistent function

To determine persistence of activity in Cushing's syndrome after transsphenoidal surgery, patients require measurement of serum and urine cortisol and plasma corticotropin levels. When patients have been successfully treated, these levels become undetectable immediately after surgery and patients require replacement treatment with hydrocortisone. If these levels decrease to within the normal range but not to suppressed levels, this usually indicates incomplete resection and predicts eventual recurrence of the disease. If patients continue to have elevated 24-hour urinary-free cortisol, elevated serum cortisol and plasma corticotropin levels, and loss of normal cortisol circadian rhythm of these hormones, by definition, they continue to have active disease. Most of these patients have persistence of clinical manifestations of active disease.

The challenge in such patients is to carefully determine if the persistence of hypercortisolemia is caused by residual tumor within the sella turcica. If the surgical specimen can be immunohistochemically confirmed to be a corticotropin-secreting adenoma, it is safe to assume that the persistence of activity is caused by residual (likely invasive) tumor. If no tumor can be identified within the sella at the time of transsphenoidal surgery, one must reconsider the original assumption that the patient had pituitary corticotropin-dependent hypercortisolemia. In this situation, it may be appropriate to perform (or repeat) a bilateral inferior petrosal sinus sampling (IPSS) to confirm whether the excess corticotropin is coming from the pituitary. If this study is negative, one should consider ectopic corticotropin syndrome, and a careful search should ensue to find the source of corticotropin. This may require chest and abdomen CT or MRI, an octreotide scan, and, in some cases, systemic selective venous sampling to seek out corticotropin gradients to help localize the regional source of excessive corticotropin secretion.

Surgical options

If a patient with persistence of function has a pathologically proven corticotropin-secreting tumor at the time of the first procedure, one of two situations generally exists. If the tumor is a microadenoma and the pituitary gland has been left intact, it may be appropriate to go back and remove all the residual tissue within the sella turcica in an attempt to provide remission. If the tumor is a macroadenoma with clear invasion into the surrounding cavernous sinuses, further resection is generally not useful. Aggressive removal of corticotropin-secreting tumors involving the pituitary stalk has proven to be useful in experienced hands [12].

If the pathologic findings from the first operation show diffuse or multifocal "hyperplasia" of pituitary corticotrophs, it is appropriate to go back and resect all the remaining gland. With hyperplasia, it is often possible to provide excellent remission with resection of all pituitary tissue.

If the original biopsy does not show tumor and the IPSS remains positive, it is mandatory to do a repeat operation to re-explore for a microadenoma or, more likely, remove the residual gland. If the patient is a woman of childbearing age, a careful

discussion must ensue to outline the available options.

If the original transsphenoidal procedure has been performed by an inexperienced surgeon, the chances are greater of effecting a remission with repeat exploration by a surgeon with greater transsphenoidal experience [13].

It is important to keep in mind that another surgical option is bilateral adrenalectomy. Although this is a procedure of last resort, it remains an excellent option for patients in whom the primary lesion cannot be completely resected or for whom medical treatment has not been completely effective [14].

Medical options

A number of medications have been tried over the years, but there are only two that are currently useful in the treatment of patients with active corticotropin-secreting adenomas. Both help to lower cortisol levels to normal. There are no drugs currently available that directly affect the pituitary adenoma.

Ketoconazole is an antifungal agent that acts as an inhibitor of steroidogenesis. This is useful in the preoperative period to control cortisol levels while awaiting surgery. It is also useful in surgical failures to help control steroid levels as patients receive other adjunctive therapy, such as radiation or adrenalectomy. The recommended dosage is 400 to 800 mg/d, although higher doses are associated with hepatotoxicity.

Mitotane is an adrenolytic drug that selectively and permanently destroys the fasciculata and reticularis zones of the adrenal cortex when given in low doses. It can be given in conjunction with pituitary irradiation and may result in permanent remission of Cushing's disease in up to 80% of patients treated for periods of 6 to 12 months [15]. It is administered in doses of 2 to 4 g/d. Treatment side effects include nausea, anorexia, lethargy, fatigue, and hypercholesterolemia, especially when high doses are given. The side effects decrease with reduction of dose.

Radiation options

Conventional fractionated external beam radiation is an important adjunct in the treatment of patients with corticotropin-secreting pituitary adenomas that fail surgical resection. Patients are candidates for radiation therapy if they have a biopsy of proven but unresectable adenoma. Radiation is usually given at a dose of 54 Gy to an area that clearly includes all the invasive aspects of the adenoma. In 1997, Estrada et al [16] reported that of 25 patients receiving pituitary irradiation, 83% enjoyed a remission, 22 of them within 2 years of treatment. The remission rate was not related to the size of the residual tumor, and there were no relapses after remission.

Focused single-dose radiosurgery has been used for more than 25 years but still has yet to be proven superior to fractionated radiation [17]. Radiosurgery is an option only in those tumors that are more than 5 mm from the optic chiasm and whose borders are readily identified on MRI.

Prolactinoma

Definition of persistent function

Because most prolactinomas are initially treated medically, persistence of activity applies to patients who fail both surgery and initial medical treatment. Because a mild elevation of prolactin has little deleterious effect compared with an elevation of GH or corticotropin, these tumors need not be treated as aggressively as those described previously. The goal of treatment of a patient with a prolactin-secreting adenoma is to control the growth of the tumor, abolish galactorrhea, and restore gonadal function if that is desired. A patient with a large invasive prolactinoma may do well over time with a mild elevation of prolactin if the tumor has been reduced in size enough to restore vision. In men, it is desirable to reduce prolactin enough to allow testosterone to return to normal, but if this is not the case, testosterone may be replaced. In women, longstanding hypogonadotropic hypogonadism that is caused by hyperprolactinemia is likely to result in a series of untoward effects, such as vaginal atrophy and osteoporosis [18]. Addition of estrogen (or an estrogen/progesterone combination in women who have a uterus) corrects these abnormalities. Microprolactinomas enlarge during pregnancy in less than 5% of cases, despite a massive increase in the estrogen milieu. Thus, small doses of estrogen are quite safe. Macroprolactinomas have a higher propensity to increase in response to estrogen, and MRI follow-up in such patients is mandatory. Watchful observation alone may be sufficient in women whose hyperprolactinemia is not accompanied by bothersome symptoms. About 10% to 20% of microprolactinomas may "disappear" both morphologically and hormonally over 5 to 10 years of observation.

Surgical options

The best surgical option exists when the patient has a microadenoma and initially opts to begin with medical treatment. If the medication fails or has too many side effects, surgical resection of a microadenoma has more than an 80% chance of normalizing prolactin. Surgery for macroprolactinomas is generally not successful at normalizing prolactin but may be necessary if the patient has optic pathway compression and fails to respond to medical therapy. Further surgery is rarely useful for those patients who fail to have a remission after their initial surgery.

Medical options

The medical options are the same for failed surgery and failed initial medical therapy. There are now three dopamine agonists available, and all are quite effective against prolactinomas. Bromocriptine (Parlodel) has been available the longest and has proven to be safe even during pregnancy. This medication is usually started at 1.25 mg/d and may be gradually increased up to 20 mg/d for large tumors. As a rule, doses above 2.5 mg twice daily are rarely needed. Bromocriptine has considerable side effects and is often not well tolerated by patients.

Pergolide (Permax) may be taken once a day by most patients and has proven to be at least as effective as bromocriptine but with fewer side effects [19]. Pergolide is usually given at 0.05 mg/d to start and may be increased significantly in patients with large or resistant tumors. Once the prolactin has fallen and the tumor is reduced in size, a lower maintenance dose of pergolide may be effective in controlling tumor growth. We have not used pergolide in women of childbearing age because it has not been approved for use during pregnancy.

Cabergoline (Dostinex) is a longer acting dopamine agonist and may be effective in treating prolactinomas at a dose of 0.5 mg once or twice a week. This medication is more expensive but has fewer side effects than bromocriptine and may be used during pregnancy [20].

Radiation options

Given the effectiveness of the medical treatment of prolactinomas, radiation is not commonly needed. There has been a large experience with radiation from earlier years [21]. Radiation quite reliably stops tumor growth, which is followed by tumor shrinkage in about 20% to 30% of cases. Normalization of prolactin levels, however, occurs only in about 20% of patients after 10 years. Thus, radiation is a legitimate option in a patient with a large and neurologically threatening tumor that does not respond to a dopamine agonist, but it should not be used as a prolactin-lowering modality. There are no data to suggest that radiosurgery has any advantage compared with conventional radiation.

Thyroid stimulating hormone-secreting adenoma

Thyroid stimulating hormone (TSH)–producing tumors cause thyrotoxicosis. As opposed to Graves' disease or nodular goiter, in TSH-induced thyrotoxicosis, elevated plasma thyroxine (T4) levels are accompanied by elevated or normal (ie, nonsuppressed) levels of TSH. Most TSH-producing adenomas are large and invasive by the time of diagnosis, and surgery is rarely fully effective in restoring the euthyroid state. Often, these tumors cosecrete GH and/or prolactin with appropriate symptomatology [22].

Definition of persistent function

Elevated plasma-free T4 and triiodothyronine (T3) concentrations constitute unequivocal evidence of persistent TSH hypersecretion. The patient may be clinically thyrotoxic even with normal thyroid hormone levels, because although nominally within the statistically defined normal range, they may be higher than the individual premorbid concentrations. In these cases, demonstration of TSH nonsuppressibility by exogenous T3 or absent TSH rise to thyrotropin-releasing hormone (TRH) may be of value [22].

Surgical options

Surgical resection of TSH adenomas is rarely if ever successful, because these tumors are usually large and invasive from the outset. Resection should be attempted only if a well-circumscribed intrasellar tumor remnant has been left behind at the initial surgery.

Medical options

Conventional modalities aimed at abolishing thyroid hormone biosynthesis (propylthiouracil or methimazole) or at destroying thyroid tissue (radioactive iodine or thyroidectomy) should not be used. The initial decline in thyroid hormone

levels is almost inevitably followed by the augmentation of TSH secretion as a result of diminished negative feedback and restoration of the thyrotoxic state. This may also expand the volume of the TSH-producing adenoma. Dopamine agonists are only rarely effective in suppressing TSH hypersecretion. Nevertheless, the convenience of oral therapy may justify a trial of these medications.

TSH-producing adenomas are exquisitely sensitive to somatostatin, and synthetic somatostatin analogues are effective in suppressing TSH hypersecretion and restoring the euthyroid state. The effective doses are usually much lower than those needed by patients with acromegaly. Often, a single daily dose (50–100 μg SC) of Sandostatin is sufficient [23]. There is some initial positive experience with longer acting preparations. As these preparations become more widely available, it is expected that most patients will receive this treatment option in the future [24].

Radiation options

There is not enough experience with radiation therapy in these relatively rare tumors to make a meaningful assessment of effectiveness. In larger series, most patients reported to have undergone radiation therapy were subsequently treated with somatostatin analogues, suggesting a low efficacy of radiation.

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