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Medical treatment of functional pituitary tumors

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The treatment of a patient with a pituitary adenoma is dependent on the type of tumor, on the effect of the tumor on vision and other features of mass effect, and on pituitary function. With the exception of a prolactin-producing adenoma, the first line of treatment for most patients is surgical removal of the mass lesion. Despite the ability to remove an adenoma completely or to debulk the lesion significantly, many patients require adjunctive medical treatment and, in some instances, pituitary radiation to control the disease. The goals of treatment include elimination of the mass effect, lowering excessive hormone production to normal, restoration of normal pituitary function, prevention of recurrence, and administration of necessary hormone replacement. This discussion addresses the indications for and results of medical therapies for functional pituitary adenomas.

Prolactin-secreting adenoma

The most common type of secretory pituitary tumor produces prolactin [1]. Hyperprolactinemia most commonly results in secondary hypogonadism in adults and primary hypogonadism in adolescents. Women of reproductive age are usually diagnosed early in the course of disease because of menstrual problems or infertility and most commonly have a microadenoma (<10 mm), whereas men and postmenopausal women tend to be diagnosed later and present with a macroadenoma (>10 mm). Thus, visual compromise from a large prolactinoma most commonly occurs in men and postmenopausal women.

Before the development of dopamine agonist therapy, the standard treatment for a prolactin-producing adenoma was surgical resection. Unfortunately, in the situation of a macroadenoma, achievement of a normal serum prolactin level with surgery occurred only in a minority of patients, on the order of 20% or less. Surgical resection of a microadenoma results in a normal serum prolactin level in approximately 80% to 90% of patients and is accompanied by restoration of normal gonadal function in most [2–5].

The hypothalamic hormone dopamine tonically inhibits prolactin synthesis and release. In the 1970s, bromocriptine, the first dopamine agonist, was developed and shown to inhibit prolactin production in hyperprolactinemic patients. This medication gained widespread use after numerous studies demonstrated that medical therapy could lower prolactin to normal, cause shrinkage of the pituitary adenoma, and restore normal gonadal function [6–8]. Thus, dopamine agonist therapy is usually considered the first line of treatment for this problem, with surgery and pituitary radiation being reserved for patients who either do not respond adequately to medical therapy, are unable to tolerate the medication, or elect to have surgery.

Currently, there are several dopamine agonist formulations available to treat hyperprolactinemia, and the selection of a particular drug depends on several factors, including side effects, ease of taking the medication, and cost. Bromocriptine is usually administered two or three times daily, always with food to minimize the risk of side effects. Pergolide is administered once or twice daily, also with food. Quinagolide, not available in the United States, is administered once daily. The most recently developed dopamine agonist, cabergoline, is long acting and is administered one to two times a week [9–11]. In the United States, only bromocriptine and cabergoline are approved by the US Food and Drug Administration (FDA) for the treatment of hypoprolactinemia. Cabergoline is not FDA approved for

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women attempting to become pregnant. The most common side effects of these medications include nausea, vomiting, orthostatic hypotension, headache, nasal stuffiness, and constipation. In a comparison of side effects and efficacy between bromocriptine and cabergoline, side effects occurred significantly less often in patients receiving cabergoline, resulting in significantly fewer dropouts from the study in cabergoline-treated patients [12]. Other comparisons between bromocriptine and cabergoline suggest that cabergoline may be more efficacious because of its long-acting stimulation of adenoma dopamine receptors and better compliance with a once- or twice-weekly regimen [13]. All the dopamine receptor agonist drugs have been shown to reduce tumor volume, thus relieving the mass effect causing visual loss and headache. A comparison of bromocriptine, pergolide, quinagolide, and cabergoline demonstrated that approximately 92% of patients achieve a substantial reduction in prolactin and shrinkage of the adenoma [14]. Other studies have demonstrated that patients who fail to respond adequately to bromocriptine therapy may be successfully treated with cabergoline [13]. Laboratory studies have demonstrated that the response to bromocriptine (and to other dopamine agonists by inference) is based on the number of and binding affinity of tumor dopamine receptors. Dopamine receptor number and binding affinity were studied in adenomas removed from patients who had a good response to bromocriptine therapy and those who failed to respond. The number of dopamine receptors and binding affinity were reduced by approximately 50% in tumors that did not respond to bromocriptine therapy [15]. The cost of the medication may be an important factor in selecting the dopamine agonist preparation. Pergolide is the least expensive of these formulations, and cabergoline is the most expensive. The desire to achieve pregnancy is also a factor in selecting which drug should be used. The greatest experience is with bromocriptine, in which several thousand women became pregnant while taking this medication. A report of more than 2000 babies born to women taking bromocriptine demonstrated that there was no increased risk above the normal risk of birth defects in babies exposed to bromocriptine early in gestation [16]. There is a more limited experience with pregnancy achieved by women taking cabergoline, but the information to date also indicates that there is no increased risk above the normal risk of birth defects in babies exposed to cabergoline [17].

As noted, a few patients do not respond to medical therapy and thus require additional treatment or treatments. Surgical debulking of a large invasive adenoma is usually performed to relieve the mass effect and to reverse visual abnormalities. This is often followed by radiation to the remaining tumor, either with conventional fractionated radiation or with stereotactic radiation (Gamma Knife [Elekta Corp, Stokholm, Sweden]; LINAC, [linear accelerator] proton beam) [18]. No form of radiation treatment produces an immediate reduction in prolactin. In one study of conventional radiotherapy, a normal serum prolactin level was achieved in 2 of 28 patients over the study period of 10 years [19]. Five of 20 patients treated with Gamma Knife radiosurgery achieved a normal serum prolactin level. Patients who received dopamine agonist therapy at the time of Gamma Knife treatment had a poorer response than those not receiving medical therapy, suggesting a radioprotective effect of a dopamine agonist [20]. Pending confirmation of this observation, it is probably prudent to withhold dopamine agonist therapy at the time of stereotactic radiation treatment and to reinstitute medical therapy afterward.

In patients who have persistent hyperprolactinemia and who desire fertility, medical therapy to induce ovulation or spermatogenesis is indicated. Women with mild persistent hyperprolactinemia may achieve ovulation with clomiphene citrate. If this is not successful, gonadotropin therapy (luteinizing hormone [LH], follicle-stimulating hormone [FSH]) may promote successful ovulation and subsequent pregnancy. In men who do not respond adequately to dopamine agonist treatment, testosterone replacement is indicated if fertility is not desired. Gonadotropin (LH, FSH) administration is necessary to stimulate endogenous testosterone production and sperm maturation; achievement of an adequate sperm count often requires more than a year of treatment.

Acromegaly

Growth hormone (GH)–secreting pituitary adenomas are usually treated first with surgical resection. An unfortunate feature of acromegaly is that the average duration of the disease before diagnosis is approximately 7 years. Thus, at the time of diagnosis, most patients have a macroadenoma, making complete surgical resection less likely. In several reports of surgical results, achievement of a normal serum insuline-like

growth factor 1 (IGF-1) level or a glucose-suppressed serum GH level of less than 1 μg/L [21] occurs in 50% to 60% of patients [22–26]. Therefore, a substantial number of patients require additional therapy. The most effective currently available medical treatment is a somatostatin analogue, which lowers serum GH and IGF-1 concentrations in approximately 90% of patients. Achievement of a normal serum IGF-1 level occurs in only approximately 50% of patients, however [27–30]. The only currently available somatostatin analogues in the United States are octreotide and Sandostatin LAR (long-acting depot octreotide). Octreotide is self-administered as a subcutaneous injection every 8 hours, and Sandostatin LAR is administered in the physician's office as an intramuscular injection in the buttock every 28 days. These formulations are equally effective. In Europe, lanreotide is also available for treatment of acromegaly. This is usually administered as an intramuscular injection every 2 weeks or as the autogel formulation, which is self-administered as a daily subcutaneous injection. Octreotide, Sandostatin LAR, and lanreotide have similar efficacy and side effects [27–36]. The most common side effect is development of gallbladder sludge or gallstones; this occurs in approximately 18% of patients [31–36]. Other side effects include loose and acholic stools, which usually resolve within 1 or 2 weeks of beginning treatment. Although the drugs are effective in controlling tumor growth, they do not usually cause dramatic shrinkage of the tumor. Approximately 30% of patients have some reduction in tumor size, usually on the order of 20% or less [37]. Thus, these medications are not usually used as primary therapy, particularly in patients who have a large adenoma. In patients with concomitant hyperprolactinemia, the combination of a somatostatin analogue and a dopamine agonist is indicated to control both GH and prolactin hypersecretion.

Although dopamine agonist treatment with bromocriptine improves clinical symptoms in most patients, reduction in serum prolactin to a normal level occurs in less than 10%. Thus, the role of this class of drugs seemed limited. Nevertheless, recent reports suggest that the long-acting dopamine agonist cabergoline may be efficacious in some patients with acromegaly, particularly in those with concomitant hyperprolactinemia [38–41].

An experimental treatment, a GH receptor antagonist, pegvisomant, acts by binding to the GH receptor, thus inhibiting generation of IGF-1 production, which is the effector of GH action. In clinical trials, pegvisomant reduced serum IGF-1 concentrations to normal in 98% of patients. This drug does not inhibit GH production and actually increases circulating GH concentrations. Additionally, there is no substantial effect on tumor size [42,43]. Of 150 patients treated with this drug, 2 developed abnormal liver transaminase levels requiring discontinuation of the medication. If this drug obtains regulatory approval for widespread use, it should be a valuable medical treatment, particularly for patients who do not respond adequately to somatostatin analogues.

Because no medical therapy causes destruction of the adenoma, pituitary radiation is often administered with a goal of achieving remission. Medical therapy is used to control GH (and prolactin) hypersecretion while awaiting the desired effects of pituitary radiation. A study of 31 patients treated with the Gamma Knife indicates that treatment with the Gamma Knife has a more prompt effect than does conventional radiotherapy, with 65% of patients apparently achieving normal serum GH and IGF-1 levels within 2 years of treatment. Of note, patients who did not receive a somatostatin analogue at the time of the Gamma Knife radiotherapy had a more prompt response than did patients receiving medical treatment at the time of Gamma Knife treatment [44]. Although this has not been confirmed in other reports, it is reasonable to withhold treatment at the time of Gamma Knife treatment in the event that this initial observation is confirmed. It is necessary to emphasize the need to achieve normal GH and IGF-1 concentrations, because persistent elevation of these hormones is associated with an ongoing risk of premature mortality [45]. Reduction in GH production to normal has been shown to reduce this risk to that of the normal population [23]. Any form of pituitary radiation may cause loss of pituitary function; thus, all patients should be monitored regularly and given appropriate hormone replacement as indicated.

Cushing's disease

There is no generally effective medical treatment to control corticotrophin hypersecretion. Medications are used to reduce adrenal cortisol production in patients with Cushing's disease, however. The antifungal agent ketoconazole in higher doses than used to treat fungal infections inhibits cortisol synthesis. Another inhibitor of cortisol synthesis is metyrapone. These medications

are most commonly employed in patients who have not achieved remission after pituitary surgery, in patients who are unable to undergo surgery, and in patients who have not been cured with surgery and who undergo pituitary radiation. Because radiation therapy is not immediately effective, it is necessary to reduce excessive cortisol levels to normal to treat the devastating symptoms and signs of Cushing's disease while awaiting the beneficial effects of pituitary radiation. Untreated Cushing's disease causes premature mortality and significant morbidity. A potentially serious side effect of ketoconazole is elevation of liver serum transaminase levels, which usually resolves with discontinuation of the drug. Because unrecognized toxicity may cause hepatic failure, patients should have liver enzymes measured before beginning treatment and periodically while receiving the medication. Patients should be instructed to report any symptoms of fatigue, nausea, or vomiting, and transaminase levels should be measured immediately. Additionally, these medications may suppress cortisol production to below normal, resulting in symptoms of adrenal insufficiency. For this reason, serum cortisol and 24-hour urine free cortisol should be monitored regularly. If the 24-hour urine free cortisol level remains elevated, the dose should be increased. If the serum cortisol level is low, a dose reduction is indicated. Because of potential hepatic toxicity, ketoconazole should not be considered for long-term therapy. A limitation of long-term metyrapone therapy is the tendency to "escape" the effects of adrenal cortisol synthesis enzyme blockade, thus requiring higher doses and the potential for eventual escape from control regardless of the dose.

An alternative to surgery followed by radiation therapy and medical therapy is bilateral adrenalectomy. This is usually reserved for patients with severe features of Cushing's disease, those unable to tolerate medical therapy, and those who prefer it. These patients should be informed of the need for lifelong glucocorticoid and mineralocorticoid replacement therapy and of the possibility of development of Nelson's syndrome. Such patients should be monitored regularly with measurement of serum corticotropin concentrations and pituitary MRI studies. In the 20% to 30% of patients with Cushing's disease who are not cured with surgery, a combination of pituitary radiation and medical therapy is usually the second choice, with bilateral adrenalectomy undertaken as a final resort.

Thyroid-stimulating hormone adenoma

Thyroid-stimulating hormone (TSH)–secreting adenomas are the least common type of secretory tumors. A TSH-secreting adenoma causes hyperthyroidism by stimulating thyroid hormone production. This type of tumor is usually treated with surgical resection, but because most are macroadenomas, complete resection may not occur. The somatostatin analogues octreotide and lanreotide have been shown to reduce TSH and thyroid hormone levels to normal and to reduce tumor size [46–49]. This medical treatment does not destroy the tumor and thus is only effective as long as it is administered [47].

Gonadotrope adenoma

Most gonadotrope adenomas do not produce excessive circulating hormone levels. Gonadotrope adenomas are most frequently diagnosed by immunohistochemistry of the surgical specimen and may be positive for LH, FSH, α-subunit, or a combination of these hormones, but serum concentrations of these hormones are normal. A few of these adenomas produce excessive serum concentrations of LH, FSH, and/or α-subunit alone or in combination. Most patients with a gonadotrope adenoma have a macroadenoma, frequently causing mass effects. The first line of therapy is surgical resection. Pituitary radiation may be employed in patients with residual tumor or in those with recurrent tumor. There have been a limited number of case reports of medical treatment with a dopamine agonist. Medical therapy with a dopamine agonist has usually been employed in patients who either refuse surgery or are not suitable medical candidates for surgery. In this small number of patients, a dopamine agonist caused a small reduction in tumor size [50–52]. There is a limited experience with the somatostatin analogue octreotide, but in a study of 4 patients with a macroadenoma producing α-subunit or clinically nonfunctioning, 3 of 4 patients had improvement in visual abnormalities without a demonstrable change in tumor size on imaging [53]. It appears that there is a limited role for medical therapy in patients with a gonadotrope adenoma whether or not there are excessive circulating hormone concentrations.

Summary

Medical therapy with a dopamine agonist is the most effective for treatment of a prolactin-

producing adenoma and is considered as primary treatment. Surgery and pituitary radiation are reserved for patients who either do not tolerate or do not respond to a dopamine agonist drug. A somatostatin analogue is effective medical therapy for patients with acromegaly, and this is usually administered if there is persistent GH hypersecretion after surgical resection. Medical treatment for patients with Cushing's disease is directed at the adrenal glands to reduce cortisol hypersecretion. Unfortunately, there is no effective medical therapy to reduce pituitary corticotropin production. Medical therapy for a gonadotrope adenoma with a dopamine agonist or somatostatin analogue has limited utility but is employed in patients who are unable to undergo surgery and may delay or prevent additional tumor growth.

Many patients with a pituitary adenoma can be successfully treated with one treatment, either a dopamine agonist for a prolactinoma or surgery for other types of tumors. A substantial number of patients require multimodality therapy, however, including medical therapy, surgery, and pituitary radiation. Because the biologic behavior of pituitary adenomas varies considerably, a patient with a pituitary adenoma requires lifelong regular monitoring for hormone hypersecretion, tumor recurrence, and development of new pituitary hormone deficiency. A coordinated plan of care among endocrinologists, neurosurgeons, neuro-ophthalmologists, and radiation therapists is necessary to provide optimal care for these patients.

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