

Diagnosis and Treatment of Pituitary Adenomas

A Review

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IMPORTANCE Pituitary adenomas may hypersecrete hormones or cause mass effects. Therefore, early diagnosis and treatment are important.

OBSERVATIONS Prevalence of pituitary adenomas ranges from 1 in 865 adults to 1 in 2688 adults. Approximately 50% are microadenomas (<10 mm); the remainder are macroadenomas (\geq 10 mm). Mass effects cause headache, hypopituitarism, and visual field defects. Treatments include transsphenoidal surgery, medical therapies, and radiotherapy. Prolactinomas account for 32% to 66% of adenomas and present with amenorrhea, loss of libido, galactorrhea, and infertility in women and loss of libido, erectile dysfunction, and infertility in men; they are generally treated with the dopamine agonists cabergoline and bromocriptine. Growth hormone-secreting tumors account for 8% to 16% of tumors and usually present with enlargement of the lips, tongue, nose, hands, and feet and are diagnosed by elevated insulin-like growth factor 1 levels and growth hormone levels; initial treatment is surgical. Medical therapy with somatostatin analogues, cabergoline, and pegvisomant is often also needed. Adrenocorticotropic hormone (ACTH)-secreting tumors account for 2% to 6% of adenomas and are associated with obesity, hypertension, diabetes, and other morbidity. Measurement of a late-night salivary cortisol level is the best screening test but petrosal sinus sampling for ACTH may be necessary to distinguish a pituitary from an ectopic source. The primary treatment of Cushing disease (hypercortisolism due to ACTH-producing adenomas, which is the cause in approximately 65% of the cases of hypercortisolism) is adenoma resection and medical therapies including ketoconazole, mifepristone, and pasireotide. Hyperthyroidism due to thyroid-stimulating hormone-secreting tumors accounts for 1% of tumors and is treated with surgery and somatostatin analogues if not surgically cured. Clinically nonfunctioning adenomas account for 15% to 54% of adenomas and present with mass effects; surgery is generally required, although incidentally found tumors can be followed if they are asymptomatic.

CONCLUSIONS AND RELEVANCE Patients with pituitary adenomas should be identified at an early stage so that effective treatment can be implemented. For prolactinomas, initial therapy is generally dopamine agonists. For all other pituitary adenomas, initial therapy is generally transsphenoidal surgery with medical therapy being reserved for those not cured by surgery.

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Approximately 10% of unselected pituitaries (meaning those from individuals without known pituitary disease) examined at autopsy contain pituitary adenomas.¹ Magnetic resonance imaging (MRI) scans of normal volunteers also show a 10% prevalence,² but other pathologic entities may have a similar appearance, such as Rathke cleft cysts and metastatic tumors.³ Not all patients with pituitary tumors develop symptoms because most tumors remain small and most do not secrete hormones in excessive amounts. Clinical case-finding studies, in which all hospitals and practices in a geographic area were queried about cases with pituitary tumors over a defined period, have suggested a prevalence of pituitary adenoma ranging from 1 in 865 persons to 1 in 2688 persons (Table 1).^{4,6-11}

Pituitary adenomas are classified into microadenomas (<10 mm), macroadenomas (\geq 10 mm), and giant adenomas (\geq 40 mm) (Figure 1).^{12,13} Pituitary carcinomas with distant metastases are rare, occurring in 0.1% to 0.2% of cases.¹² If an MRI shows the tumor impinging on the optic chiasm, then formal visual field testing is indicated.¹³ An evaluation for hypopituitarism should be carried out in all patients with macroadenomas and even large (6-9 mm) microadenomas.¹ Diabetes insipidus is rarely seen with pituitary adenomas.¹

About two-thirds of pituitary adenomas may secrete excess hormones. In the studies^{4,6-11} that included 1718 patients, about 50% of cases were macroadenomas and 32% to 66% of tumors were secreting prolactin, 14% to 54% were clinically nonfunction-

Table 1. Prevalence of Pituitary Adenomas in Community-Dwelling Adults

Source	Country	Years of Data Collection	No. of Patients With Pituitary Adenomas	Prevalence	No. of Patients (%)				
					Prolactin-Secreting Tumor	CNFA	Growth Hormone-Secreting Tumor	ACTH-Secreting Tumor	Macroadenomas
Daly et al, ⁴ 2006	Belgium	2005	68	1/1064	45 (66) ^{a5}	10 (15)	9 (13)	4 (6)	29 (43)
Fontana et al, ⁶ 2009	Switzerland	2006-2007	44	1/1241	25 (56)	13 (30)	4 (9)	2 (4)	19 (44)
Fernandez et al, ⁷ 2010	England	2006	63 ^b	1/1289	36 (57)	18 (28)	7 (11)	1 (2)	26 (41)
Raappana et al, ⁸ 2010	Finland	1992-2007	164 ^b	1/1471	84 (51)	59 (37)	14 (8)	5 (3)	75 (46)
Gruppetta et al, ⁹ 2013	Malta	2000-2011	316 ^b	1/1321	146 (46)	108 (34)	52 (16)	7 (2)	136 (43)
Tjörnstrand et al, ¹⁰ 2014	Sweden ¹⁰	2001-2011	592 ^b	1/2688	187 (32)	320 (54)	53 (9)	25 (4)	384 (65)
Agustsson et al, ¹¹ 2015	Iceland	1955-2012	471	1/865	188 (40)	203 (43)	53 (11)	27 (6)	259 (55)

Abbreviations: ACTH, adrenocorticotropic hormone; CNFA, clinically nonfunctioning adenomas.

^a Number of adenomas of this type (percentage of total number of adenomas).

^b In the series from England, there was 1 case that could not be classified; in the series from Finland, there were 2 cases that had thyrotropin-secreting

adenomas; in the series from Malta, there were 3 cases that had thyrotropin-secreting adenomas; in the series from Sweden, there were 4 cases that had thyrotropin-secreting adenomas, 1 case that had a gonadotropin-secreting adenoma, and 2 cases that could not be classified.

ing adenomas, 8% to 16% were secreting growth hormone, 2% to 6% were secreting adrenocorticotropic hormone (ACTH), and less than 1% were secreting thyrotropin (Table 1). Although most clinically nonfunctioning adenomas stain for gonadotropins or their subunits, on rare occasions they stain for growth hormone, ACTH, or prolactin but do not secrete these hormones in excess. These adenomas are referred to as "silent" somatotroph, corticotroph, or lactotroph tumors.¹⁴

The pathogenesis of most pituitary adenomas remains unknown.¹⁵ Fewer than 5% of adenomas have defined pathogenetic mutations although this is an emerging field. Therefore, genetic evaluation is not warranted for patients presenting with adenomas unless there is a compatible family history.¹⁵

Transsphenoidal surgical adenoma resection is the initial treatment chosen for all tumors except prolactinomas. Rarely is craniotomy performed.^{16,17} With expert pituitary surgeons, remission rates can be achieved in 80% to 90% of patients with microadenomas and 40% to 70% of those with macroadenomas, with a 10% to 20% recurrence rate because of regrowth of tumor remnants over several years.¹⁷ Complication rates decrease with increased experience of the neurosurgeon and are approximately for carotid artery injury, 0.4%; central nervous system injury, 0.6%; loss of vision, 0.5%; ophthalmoplegia, 0.4%; cerebrospinal fluid leak, 1.5%; meningitis, 0.5%; hypopituitarism, 7.2%; diabetes insipidus, 7.6%; death, 0.2%.^{18,19} Even with experienced neurosurgeons, delayed hyponatremia occurring 7 to 10 days postoperatively can occur in 4% to 10% of patients due to inappropriate vasopressin secretion.²⁰

Irradiation is reserved for patients who do not achieve adequate reduction in tumor size, hormone levels, or both in response to surgery, medical therapy, or both.^{21,22} The older conventional fractionated therapy has largely been abandoned in favor of giving high-dose irradiation in a single visit or a few visits after careful stereotactic mapping of the tumor, except in the case of large, invasive tumors or those in close proximity to the optic chiasm.^{21,22}

Stereotactic radiotherapy results in overall faster reduction in hormone secretion and fewer adverse effects than conventional radiotherapy, although the risk for hypopituitarism remains high for both types of radiotherapy, reaching 20% by 5 years and 80% by 10 to 15 years.^{21,22}

Prolactinoma (Prolactin-Secreting Tumor)

Prolactinomas comprise close to 50% of all pituitary adenomas in most series^{4,6-11} and occur most frequently among women aged 20 to 50 years.²³ Prolactin is normally inhibited by the neurotransmitter dopamine coming from the hypothalamus, so that hypothalamic or pituitary stalk disease may cause a decrease in this inhibition and a rise in prolactin levels. Many medications block dopamine receptors and can also cause prolactin elevations (Box). A number of other conditions can also raise prolactin levels, such as pregnancy, hypothyroidism, and renal insufficiency (Box).

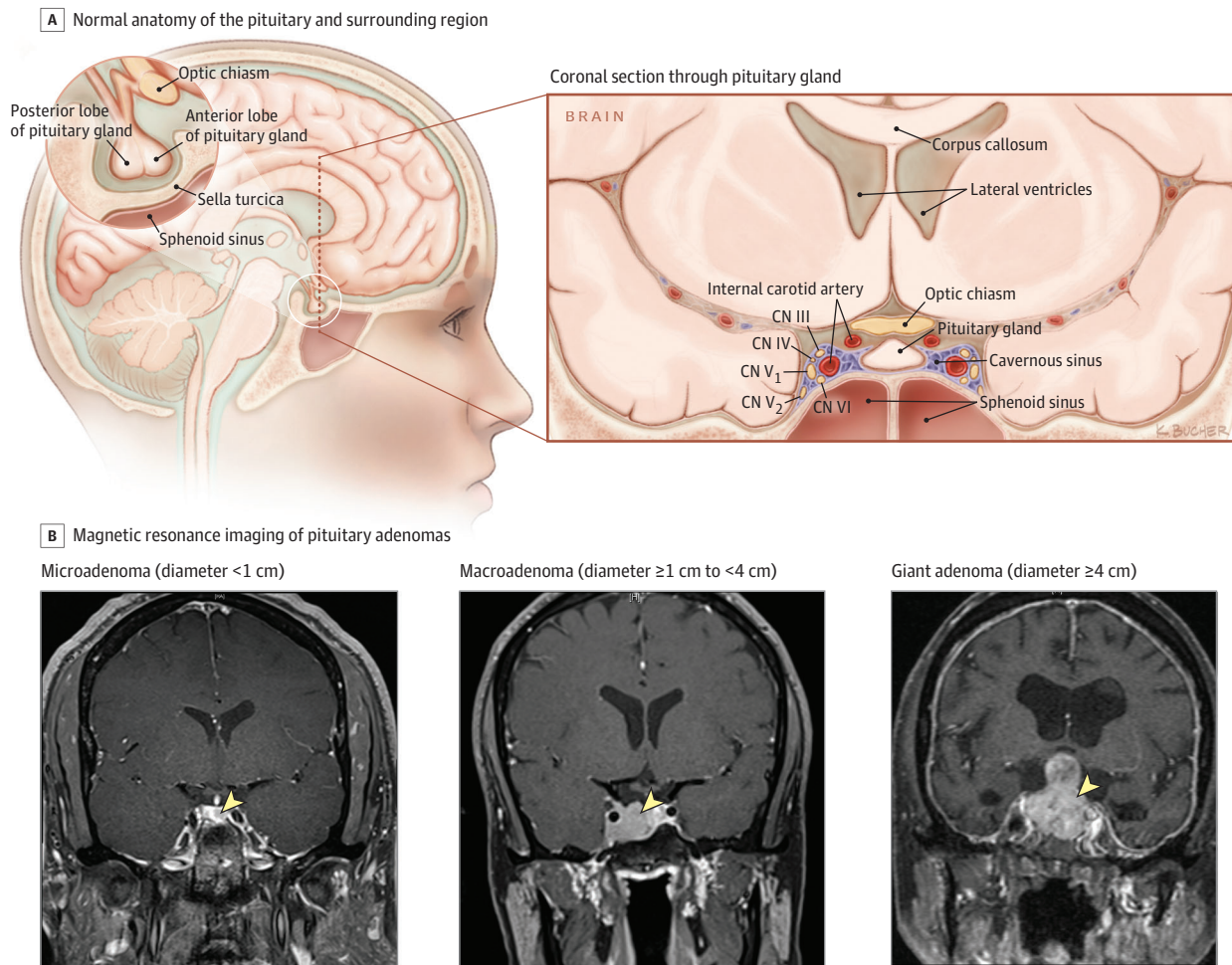
Presentation

Elevated prolactin levels suppress the hypothalamic-pituitary-gonadal axis, resulting in loss of libido, infertility, and osteoporosis in both sexes, oligomenorrhea or amenorrhea and galactorrhea in women and erectile dysfunction in men.²³⁻²⁵ Macroadenomas may cause additional symptoms related to tumor size.

Evaluation and Diagnostic Testing

Since there are causes of hyperprolactinemia other than prolactinoma (Box) a careful history, examination, and measurement of serum thyrotropin and creatinine are required.^{23,24} An MRI will determine whether a tumor is present and its size. More than 90% of prolactinomas are microadenomas.⁷ If no tumor is found, the hyperprolactinemia is idiopathic. Non-prolactin-producing macroadenomas can cause prolactin elevations from disinhibition of prolactin secretion by compressing the pituitary stalk or hypothalamus. If the prolactin level is more than 200 µg/L (to convert to pmol/L, multiply by 43.478), it is almost always due to production by

Figure 1. Anatomy Surrounding the Pituitary Gland and Magnetic Resonance Imaging of Pituitary Adenomas



CN indicates cranial nerve. Yellow arrows indicate location of adenomas.

a prolactinoma rather than stalk compression.²⁶ If the tumor is very large (>3 cm), the very high prolactin levels (usually >10 000 µg/L) may rarely saturate the antibodies in some assays, leading to artifactually low or normal results (the “hook effect”) and prolactin levels should be rerun at 1:100 dilution to exclude this.^{24,25}

Treatment

The goals of treatment are to restore normal gonadal function and fertility and reduce tumor size for patients with macroadenomas.^{24,25} For patients with minimal symptoms who are eugonadal (eg, women with mild galactorrhea and regular menses) and have normal MRI scans or microadenomas, observation alone can be done, monitoring prolactin levels every 6 to 12 months. If prolactin levels increase or symptoms due to the hyperprolactinemia develop, a repeat MRI may be done to assess tumor size and treatment initiated.^{24,25} Only 5% to 10% of microprolactinomas enlarge over 10 years.²³ For women with oligomenorrhea or amenorrhea who do not wish to become pregnant, estrogen in the form of oral contraceptives or other estrogen plus progestin regimens are a reasonable therapeutic option.^{24,25}

Most patients with prolactinomas are treated with dopamine agonists, which activate dopamine receptors on the tumors, because of their high efficacy and tolerability; cabergoline has been shown to be more effective in normalizing prolactin levels and reducing tumor size with fewer adverse effects than bromocriptine.²³⁻²⁵ About 15% to 20% of patients, especially those with macroadenomas, may require higher than conventional doses ($\ge 2\text{ mg/week}$) to achieve control.^{27,28} Although a 3- to 6-fold increased risk of cardiac valvular abnormalities has been found among patients with Parkinson disease who receive very high doses of cabergoline (3-5 mg/d) for more than 6 months,²⁹ this adverse effect does not occur among patients with prolactinomas treated with conventional doses.³⁰ However, because the threshold dose for causing valvular risk is unknown, echocardiograms should be obtained yearly in the subset of patients exceeding a weekly dose of 2 mg.³¹ Another adverse effect of dopamine agonists, occurring in about 5% of patients, is compulsive behavior, such as excessive gambling and hypersexuality. Patients should be cautioned against this adverse effect.³²

Transsphenoidal surgery is a therapeutic option and can achieve a normalization of prolactin in 65% to 85% of patients with

microadenomas and 30% to 40% with macroadenomas with recurrence rates of 20% over 10 years.²³ Radiotherapy is generally reserved for the uncommon patients (<5%) whose hyperprolactinemia and tumor cannot be controlled with dopamine agonists or surgery.^{24,25} The alkylating agent, temozolomide, has been used for very aggressive prolactinomas and pituitary carcinomas with limited success.³¹

Pregnancy

The high estrogen levels of pregnancy have a stimulatory effect on lactotroph cells, resulting in risks of tumor growth of 21% for those with preexisting macroadenomas and of 2% to 3% for those with preexisting microprolactinomas.³³ Both dopamine agonists are safe to use in early pregnancy³³ and are considered US Food and Drug Administration (FDA) class B (no evidence for risk in humans) for pregnant women. Nonetheless, for women with prolactinomas being treated with dopamine agonists, these drugs are usually stopped when a woman becomes pregnant and reinstated if tumors enlarge significantly (causing severe headaches or visual field defects). In the very rare circumstance of no response to the dopamine agonist and worsening vision, transsphenoidal surgery or delivery (if the pregnancy is far enough advanced) should be performed.³³

Acromegaly (Growth Hormone–Secreting Tumor)

More than 95% of patients with acromegaly have a growth hormone–producing pituitary adenoma.³⁴ In less than 5% of cases, acromegaly may be due to a neuroendocrine tumor producing growth hormone–releasing hormone.³⁵ The increased secretion of growth hormone stimulates production of insulin-like growth factor 1 (IGF-1) from the liver and other tissues.³⁴

Presentation

Growth hormone oversecretion results in systemic complications (including diabetes mellitus, hypertension, arthritis, carpal tunnel syndrome, sleep apnea, and enlargement of hands and feet) and changes in facial features (such as prognathism; tongue, lip, and nose enlargement; and forehead prominence).^{34,36} Gigantism (excessive height) occurs if the growth hormone excess begins prior to the closure of the epiphyses during puberty.³⁴ Acromegaly is associated with a 2-fold increase in mortality, primarily due to cardiovascular disease, that is reversed with therapy that controls the hormone oversecretion.³⁷ Patients are usually diagnosed when they present with an acromegaly-associated comorbidity.^{34,38}

Evaluation and Diagnostic Testing

Initial screening consists of measuring an IGF-1 level. An elevated, age-adjusted IGF-1 level is 90% specific for a growth hormone–secreting pituitary adenoma.³⁸ Because growth hormone is secreted in a pulsatile fashion, a growth hormone level less than 10 µg/L in a single sample is not diagnostic. If clinical signs are equivocal and the IGF-1 level is not very high, an oral glucose tolerance test should be performed to demonstrate that growth hormone levels cannot be suppressed to less than 1 µg/L by hyperglycemia.³⁸ An MRI should next be performed to assess tumor size and invasiveness. About two-thirds of growth hormone–secreting tumors are macroadenomas.³⁴

Any morbidities due to the elevated growth hormone level, such as diabetes and hypertension need to be treated appropriately.³⁸

Box. Etiologies of Hyperprolactinemia

Pituitary disease

- Prolactinomas
- Acromegaly
- Empty sella syndrome
- Lymphocytic hypophysitis
- Cushing disease

Hypothalamic disease

- Craniopharyngiomas
- Meningiomas
- Dysgerminomas
- Nonsecreting pituitary adenomas
- Other tumors
- Sarcoidosis
- Langerhans cell histiocytosis
- Neuraxis irradiation
- Vascular
- Pituitary stalk section

Medications

- Phenothiazines
- Haloperidol
- Atypical antipsychotics
- Monoamine-oxidase inhibitors
- Tricyclic antidepressants
- Reserpine
- Methyl dopa
- Metoclopramide
- Verapamil
- Serotonin reuptake inhibitors

Neurogenic

- Chest wall lesions
- Spinal cord lesions
- Nipple stimulation

Other

- Pregnancy
- Hypothyroidism
- Chronic kidney disease
- Cirrhosis
- Pseudocystitis
- Adrenal insufficiency

There is an increased risk for colon neoplasia (odds ratios [ORs]: hyperplastic polyps, 3.7; colon adenomas, 2.537; colon cancer, 4.351) and a colonoscopy should be performed around the time of diagnosis.^{39,40} There can be cardiac valvular disease and rarely an acromegalic cardiomyopathy, so an echocardiogram may be helpful.^{36,38} Sleep apnea is common and appropriate assessment and treatment can be helpful.^{36,38} There are also increased risks of thyroid nodules (OR, 3.6) and thyroid cancer (OR, 7.9) among people with acromegaly, so a thyroid ultrasound may also be helpful.⁴¹

Table 2. Medications Used for the Treatment of Pituitary Adenomas

Medication	Dose	Drug Class	Patients Achieving Hormonal Control, % ^a	Adverse Effects
Prolactin-Secreting Tumor ^{23-25,27}				
Bromocriptine	2.5-7.5 mg/d	Dopamine agonist	60-80	Nausea, vomiting, constipation, dizziness, headache, compulsive behavior
Cabergoline	0.5-2.0 mg/wk	Dopamine agonist	80-90	Nausea, vomiting, constipation, dizziness, headache, compulsive behavior, cardiac valve disorders (high doses [$>2\text{mg/wk}$])
Growth Hormone-Secreting Tumor (Acromegaly) ^{34,38,42,45-53}				
Cabergoline	0.5-2.0 mg/wk	Dopamine agonist	32	Nausea, vomiting, constipation, dizziness, headache, compulsive behavior
Octreotide LAR	10-30 mg/mo	Somatostatin analog	20-35	Abdominal cramps, flatulence, diarrhea, gall bladder stones and sludge, alopecia
Lanreotide depot	60-120 mg/mo	Somatostatin analog	20-35	Abdominal cramps, flatulence, diarrhea, gall bladder stones and sludge, alopecia
Pasireotide LAR	20-60 mg/mo	Somatostatin analog	30-40	Abdominal cramps, flatulence, diarrhea, gall bladder stones and sludge, alopecia, worsening of diabetes
Pegvisomant	10-20 mg/d	Growth hormone receptor blocker	63-90	Hepatotoxicity, nausea, diarrhea
Adrenocorticotropic Hormone-Secreting Tumor (Cushing Disease) ⁵⁴⁻⁶⁴				
Ketoconazole	200-1200 mg/d	Enzyme inhibitor	49	Hepatotoxicity, nausea, dizziness, diarrhea, rash, hypogonadism in men
Cabergoline	1-3 mg/wk	Dopamine agonist	32	Nausea, vomiting, constipation, dizziness, headache, compulsive behavior
Mifepristone	300-1200 mg/d	Cortisol receptor blocker	60-87 ^b	Adrenal insufficiency, hypokalemia, menorrhagia, edema
Pasireotide	600-900 μg bid	Somatostatin analog	26	Abdominal cramps, flatulence, diarrhea, gall bladder stones and sludge, alopecia, worsening of diabetes
Etomidate	0.04-0.05 mg/kg/h	Enzyme inhibitor	100	Sedation (avoid overdose [$>0.1\text{ mg/kg/h}$], which will cause apnea and somnolence)
Metyrapone	500-4000 mg/d	Enzyme inhibitor	50-76	Hirsutism, acne, hypokalemia, hypertension
Thyrotropin-Secreting Tumor (Adenomas) ^{65,66}				
Octreotide LAR	10-30 mg/mo	Somatostatin analog	90	Abdominal cramps, flatulence, diarrhea, gall bladder stones and sludge, alopecia
Lanreotide depot	60-120 mg/mo	Somatostatin analog	90	Abdominal cramps, flatulence, diarrhea, gall bladder stones and sludge, alopecia

Abbreviations: LAR, long-acting release.

^a Achieving hormonal control was defined as normal prolactin levels for prolactin-secreting tumors, normal insulin-like growth factor 1 levels (adjusted for age) and growth hormone levels less than 1.0 $\mu\text{g/L}$ for

growth hormone-secreting tumors, normal urinary-free cortisol for adrenocorticotropic hormone-secreting tumors, and normal thyroxine and triiodothyronine levels for thyrotropin-secreting tumors.

^b Symptomatic control. Cortisol levels cannot be used to assess control.

Treatment

The goals of treatment are first to achieve biochemical control, defined as a reduction in growth hormone levels to less than 1 $\mu\text{g/L}$ and IGF-1 levels to the normal age-adjusted range, which eliminates the excess mortality and reduces the morbidity of acromegaly and also to reduce or eliminate tumor mass.³⁸ Transsphenoidal surgery is recommended as primary therapy.³⁸ Expert pituitary neurosurgeons can achieve these therapeutic goals in 80% to 90% of patients with microadenomas and 40% to 60% of those with macroadenomas.^{38,42,43} The 5-year recurrence rate is approximately 2% to 8%.³⁸ Repeat IGF-1 levels and growth hormone levels during an oral glucose tolerance test should be obtained about 12 weeks following surgery, along with an MRI to assess the changes in tumor size.³⁸

A repeat surgery to remove more tumor tissue can result in biochemical control in about 50% of patients.^{38,44} Cabergoline can achieve biochemical control in about one-third of patients with mild elevations of growth hormone and IGF-1 levels (Table 2).⁴⁵ The somatostatin analogues octreotide long-acting release and lanreotide depot can achieve biochemical control in 20% to 35% of patients.^{38,46-49} Cabergoline added to somatostatin analogues can further improve therapeutic success in 52% of patients.⁴⁵

Pasireotide has greater efficacy than octreotide and can be tried if the response to octreotide is poor.⁴⁸ Adverse effects of somatostatin analogues include gallbladder stones and sludge, abdominal cramps, flatulence, and diarrhea.³⁸ In addition, pasireotide causes a worsening of glucose tolerance and diabetes in 50% to 70% of patients.⁴⁸ Pegvisomant, a growth hormone receptor antagonist, normalizes IGF-1 levels in 60% to 80% of patients.^{50,51} It does not have any direct effects on the tumor to reduce growth hormone levels or tumor size.^{50,51} Pegvisomant can be used alone or in combination with somatostatin analogues⁵² and cabergoline.⁵³

Cushing Disease (ACTH-Secreting Tumor)

Hypercortisolism (Cushing syndrome) can be due to ACTH production by a pituitary adenoma (Cushing disease); ectopic production of ACTH or corticotropin-releasing hormone by neuroendocrine neoplasms; or ACTH-independent cortisol overproduction by adrenal adenomas and adrenal carcinomas; or exogenous glucocorticoids.⁶⁷ An ACTH-producing adenoma is the cause in about 65% to 70% of cases.⁶⁷ Cushing syndrome is associated with a 2- to 5-fold increase in mortality⁶⁸ that is largely reversed with curative treatment although substantial morbidity related to the diabetes and cardiovascular disease may persist.⁶⁸

Presentation

Patients generally present with 1 or more comorbidities associated with hypercortisolism (including weight gain, redistribution of fat resulting in centripetal obesity and increased supraclavicular and dorsocervical fat pads, facial rounding and plethora, violaceous skin striae and ecchymoses, diabetes mellitus, hypertension, mood disorders [especially depression], and osteoporosis).⁶⁷

Evaluation and Diagnostic Testing

The initial step is to confirm that hypercortisolism is present, after excluding exogenous steroid use.⁶⁹ The test with the best sensitivity and specificity (92%-100% for each) is the late-night salivary cortisol level,^{69,70} which is elevated because the marked diurnal variation in ACTH and cortisol secretion is lost with Cushing syndrome. An overnight 1 mg dexamethasone test has 95% sensitivity and 80% specificity when using a cortisol cutoff of 1.8 µg/dL (to convert to nmol/L, multiply by 27.588).⁶⁹ Women receiving oral estrogens may have increased corticosteroid-binding globulin levels and total cortisol levels above that threshold, yielding false-positive results.⁶⁸ The 24-hour urinary-free cortisol measurement has lower sensitivity and specificity and false-positive results may be seen with high fluid intake and urine output, depression, excessive alcohol intake, and other conditions.⁶⁹ Often more than 1 test is done to establish that hypercortisolism is present.⁶⁹

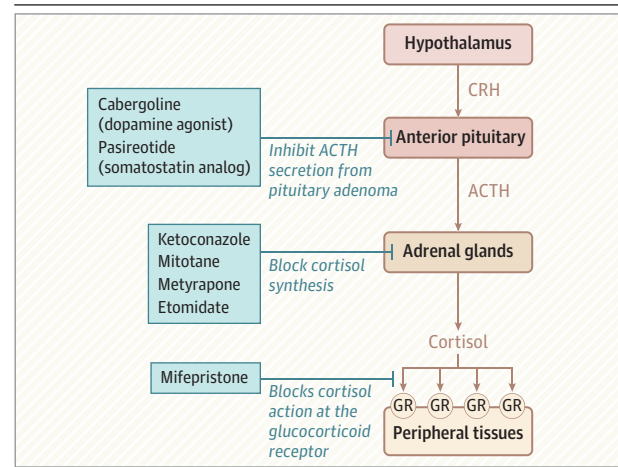
The next step is to determine the etiology of the hypercortisolism. ACTH levels are low if there is autonomous production by the adrenal gland and the levels are not suppressed or even elevated if a pituitary tumor or ectopic ACTH or corticotropin-releasing hormone production is the cause. More than 80% of ACTH-secreting pituitary adenomas are microadenomas, and the MRI may be normal in up to 50% of cases.⁶⁷ In some cases, to differentiate between a pituitary vs an ectopic source of ACTH, inferior petrosal sinus sampling is done, in which catheters are threaded up to the petrosal sinuses that drain the pituitary venous system. ACTH levels are measured from each petrosal sinus and peripherally before and after stimulation with corticotropin-releasing hormone to look for a 3-fold central step-up, which indicates Cushing disease.^{69,70}

Treatment

Transsphenoidal surgery is the initial preferred treatment for patients with Cushing disease caused by pituitary adenomas with cure rates in the 80% to 90% range by expert pituitary surgeons and a recurrence rate of 10% to 20%.^{54,71,72} If patients are not cured, then options include repeat surgery, associated with a 50% success rate,⁷³ medical therapy, pituitary irradiation, or bilateral adrenalectomy.⁵⁵ Irradiation may take 2 to 5 years to be effective⁷⁴ and medical therapy would be required to bring the hypercortisolemic state under control to improve morbidity and mortality.

Medical therapy can be directed at the adrenal glands, at the pituitary tumor, and at the glucocorticoid receptor in peripheral tissues (Figure 2).⁵⁶ Ketoconazole blocks several steps in cortisol synthesis, resulting in a normalization of cortisol levels in about 50% of patients (Table 2).⁵⁷ In 2013, the FDA specified a "black box warning" regarding liver toxicity with ketoconazole use.⁵ The risk for acute liver failure with ketoconazole is only 2.9 per 1000 patient-years.⁷⁵ Cabergoline can normalize cortisol levels in about one-third of patients with Cushing disease.⁵⁸ Neither

Figure 2. Sites of Action for the Various Medications Used for the Treatment of Cushing Disease



CRH indicates corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; GR, glucocorticoid receptor.

ketoconazole nor cabergoline have FDA indications for this use.⁵⁶ Pasireotide acts on somatostatin receptors on corticotroph adenomas and was able to normalize cortisol levels in 19% of patients but also caused a worsening of glucose tolerance in 73%.⁵⁹ Mifepristone, a progesterone receptor antagonist and abortifacient (RU-486), is also a glucocorticoid receptor antagonist that improves glucose tolerance, body weight, and quality of life.⁶⁰ Menorrhagia may occur due to endometrial hyperplasia.^{60,61} Monitoring of mifepristone treatment can be difficult because ACTH and cortisol levels increase rather than decrease and overdosing causing adrenal insufficiency can occur. If severe adrenal insufficiency occurs, large doses of dexamethasone (10 mg) may be necessary because of the receptor blockade.⁶¹

Metyrapone inhibits the enzyme that converts 11-deoxycortisol to cortisol and can control cortisol levels in 50% to 76% of patients.⁶² Mitotane is an adrenolytic agent and is used to treat adrenal cancer⁶³; in patients with ACTH-secreting adenomas, normal urine-free cortisol levels can be achieved in 57% but gastrointestinal and neurologic adverse effects are very common.⁶³ Etomidate, an anesthetic agent, blocks several steps in cortisol synthesis and is given intravenously for the treatment of severe hypercortisolemia in the critically ill patient.⁶⁴ Combinations of some of these medications can be effective in small numbers of patients not responsive to single agents.⁵⁶

Another therapeutic option is bilateral, laparoscopic adrenalectomy, which offers the benefit of immediate cessation of hypercortisolism. However, this results in life-long adrenal insufficiency and a 50% risk of pituitary tumor enlargement (Nelson syndrome).⁵⁵

Thyrotropin-secreting adenomas comprise less than 1% of pituitary adenomas^{4,6-11} and present as clinical hyperthyroidism, including a goiter, with laboratory testing revealing elevated thyroxine and triiodothyronine levels but a normal or elevated thyrotropin level instead of the usual suppressed thyrotropin level seen with autonomous thyroid disease (such as Graves disease).^{65,66} Most thyrotropin-secreting adenomas are macroadenomas and about 25% co-secrete growth hormone or prolactin.⁶⁵ Transsphenoidal surgery is carried out after medical treatment with antithyroid agents

(such as methimazole and propylthiouracil) have rendered the patient euthyroid.^{65,66} Patients not cured by surgery can be treated with somatostatin analogs (which can normalize thyrotropin and thyroid hormone levels in more than 90% of patients and tumor size reduction in more than 40% of patients) and by irradiation.^{65,66}

Clinically Nonfunctioning Adenomas

Clinically nonfunctioning adenomas (defined as no secretion of excess hormones) comprise about one-third of pituitary adenomas^{4,6-11} and range from being completely asymptomatic (and therefore detected as incidental findings [incidentalomas] on MRI or computed tomography scans performed for other reasons) to causing significant hypothalamic or pituitary dysfunction and visual or other symptoms due to their large size.^{1,76,77} In the 9 series that reported 454 patients with pituitary incidentalomas,⁷⁸⁻⁸⁶ 304 patients (67%) had macroadenomas. This is in sharp contrast to autopsy data, which show that macroadenomas comprise less than 1% of incidental tumors at autopsy, suggesting that there may be some connection between the presence of an "incidental" macroadenoma and the symptom(s) that caused the MRI to be done.

Presentation

Most patients with clinically nonfunctioning adenomas present with symptoms of mass effect, such as headaches, visual field defects, ophthalmoplegias, and hypopituitarism.¹ By definition, pituitary incidentalomas do not present with symptoms due to the tumor. Most incidentalomas do not grow over time. In the 9 series⁷⁸⁻⁸⁶ plus patients from 2 additional series with patients with clinically nonfunctioning adenomas that were not treated surgically,^{87,88} of 166 patients with microadenomas, only 17 patients (10%) experienced tumor growth and of the 356 patients with macroadenomas, only 86 patients (24%) showed evidence of tumor enlargement, on follow-up MRI scans over an 8-year period.¹ Tumor volume-doubling periods range from 0.8 to 27.2 years,⁸⁹ emphasizing the tremendous variability in tumor rates of growth.

Evaluation and Diagnostic Testing

Patients who have pituitary incidentalomas should be evaluated for hormone oversecretion by the methods discussed for each specific tumor type. If oversecretion is found, treatment should be instituted as appropriate.^{76,77} All patients with clinically nonfunctioning adenomas that are macroadenomas and larger microadenomas (eg, ≥ 6 mm), whether symptomatic or incidental, should be evaluated for hypopituitarism.^{76,90} Hyperprolactinemia may occur because of pituitary stalk dysfunction. Visual field testing is indicated when the MRI shows the tumor abutting the optic chiasm.

Treatment

Transsphenoidal resection usually is recommended for patients with enlarging tumors or tumors symptomatic with mass effects.^{1,77} Resolution of 1 or more hormonal deficits by surgery can be expected in 15% to 50% of patients with resolution of hyperprolactinemia in more than two-thirds of patients.¹ Conversely, surgery may induce an additional loss of 1 or more pituitary hormones when they were normal preoperatively in 2% to 15% of patients.¹ Postoperative MRIs done at 3 months and then yearly will assess for residual tumors and regrowth of any tumor remnants.⁷⁷

Radiotherapy as primary therapy is rarely done and mainly restricted to those patients who would not be able to tolerate surgery. More commonly, radiotherapy is given as adjunctive therapy postoperatively when residual tumor is present on MRI. Outcome data show that tumor regrowth for those patients with no visible tumor on postoperative MRI, occurred in 7.1% who received routine conventional radiotherapy and in 14% who did not receive routine radiotherapy. For those who had visible tumor on postoperative MRI, 11.2% who received routine conventional radiotherapy and 50.1% who did not receive routine radiotherapy experienced growth of tumor remnants.¹ In a review summarizing 28 series in which 904 patients with clinically nonfunctioning adenomas were treated with newer stereotactic techniques, tumor growth was controlled in 88% to 97%, but this was only over a 4-year period.⁹¹

Only 10% of people with incidentalomas that are microadenomas experience tumor growth. Therefore, surgical resection is generally not indicated, and yearly repeat scanning for 2 to 3 years to detect tumor enlargement should be performed; subsequently this can be done at less-frequent intervals, based on expert opinion.⁷⁶ Surgery is done only for significant tumor enlargement.^{76,77} Incidentalomas of 1 cm or more in diameter have already indicated a propensity for growth. Visual field defects and severe headaches are indications for surgery, and hypopituitarism is a relative indication for surgery.^{76,77} If a tumor is found to abut the optic chiasm, even though testing shows normal visual fields, consideration should be given to surgery,⁷⁶ but, if surgery is not done, visual fields should be monitored at 6-month to 12-month intervals.^{76,77} A completely asymptomatic macroadenoma can be followed with repeat yearly scans, surgery being deferred unless there is evidence of tumor growth.⁷⁶ Hemorrhage into these tumors is uncommon but anticoagulation may predispose patients to this complication.^{1,76} Dopamine agonists have been shown to decrease tumor growth in some series.^{92,93}

Discussion

About one-half of pituitary tumors that present clinically are macroadenomas,^{4,6-11} and these patients should have a careful evaluation for hypopituitarism and assessment for visual field defects if the tumor abuts the optic chiasm. For hormone-secreting adenomas, other causes of elevated hormone levels must be excluded and then specific testing should be done to document autonomous tumor hormone production. Dopamine agonists are the initial treatment for patients with prolactinomas.²³⁻²⁵ They are highly effective in normalizing prolactin levels and reducing tumor size.²³⁻²⁵ For all other hormone-secreting or nonfunctioning macroadenomas, transsphenoidal selective adenoma resection by an expert pituitary neurosurgeon is recommended as the initial treatment.^{38,54,77} For patients in remission following surgery, continued surveillance with MRI scans and hormone levels should be carried out to detect tumor recurrence or regrowth for up to 20 years following surgery. For those not in remission after surgery, medical therapies should be prescribed that are directed at the tumor, the major target organ (the adrenal gland in Cushing disease), or at hormone receptors that are specific to the tumor type.^{38,54,77} Irradiation should be reserved for patients whose tumors, hormone levels, or both are not controlled by surgery and medical treatment.^{25,38,54,77}

Although genetic mutations are associated with some tumor types, the pathogenesis of more than 95% of tumors is still unknown. As more mutations are identified along with a better understanding of tumorigenesis, additional medical treatments may be developed targeting specific stages of tumor development. Although a number of medical treatments have been developed for many of the adenomas, there are very few head-to-head comparisons of therapeutic efficacy in randomized clinical trials and such trials are needed.

Conclusions

Patients with pituitary adenomas should be identified at an early stage so that effective treatment can be implemented. For prolactinomas, initial therapy is generally dopamine agonists. For all other pituitary adenomas, initial therapy is generally transsphenoidal surgery with medical therapy being reserved for those not cured by surgery.

ARTICLE INFORMATION

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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