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is associated with decreased libido and potency, infertility, decreased muscle mass with weakness, reduced beard and body hair growth, soft testes, and characteristic fine facial wrinkles. Osteoporosis occurs in both untreated hypogonadal women and men.

■ ■LABORATORY INVESTIGATION Central hypogonadism is associated with low or inappropriately normal serum gonadotropin levels in the setting of low sex hormone concentrations (testosterone in men, estradiol in women). Because gonadotropin secretion is pulsatile, valid assessments may require repeated measurements or the use of pooled serum samples. Men have reduced sperm counts. PART 12 Endocrinology and Metabolism Intravenous GnRH (100 μg) stimulates gonadotropes to secrete LH (which peaks within 30 min) and FSH (which plateaus during the ensuing 60 min). Normal responses vary according to menstrual cycle stage, age, and sex of the patient. Generally, LH levels increase about threefold, whereas FSH responses are less pronounced. In the setting of gonadotropin deficiency, a normal gonadotropin response to GnRH indicates intact pituitary gonadotrope function and suggests a hypo thalamic abnormality. An absent response, however, does not reliably distinguish pituitary from hypothalamic causes of hypogonadism. For this reason, GnRH testing usually adds little to the information gained from baseline evaluation of the hypothalamic-pituitary-gonadotrope axis except in cases of isolated GnRH deficiency (e.g., Kallmann syndrome). MRI examination of the sellar region and assessment of other pituitary functions usually are indicated in patients with documented central hypogonadism. TREATMENT Gonadotropin Deficiency In males, testosterone replacement is necessary to achieve and maintain normal growth and development of the external genitalia, secondary sex characteristics, male sexual behavior, and androgenic anabolic effects, including maintenance of muscle function and bone mass. Testosterone may be administered by intramuscular injections every 1–4 weeks or by using skin patches or testoster one gels (Chap. 403). Gonadotropin injections (hCG or human menopausal gonadotropin [hMG]) over 12–18 months are used to restore fertility. Pulsatile GnRH therapy (25–150 ng/kg every 2 h), administered by a subcutaneous infusion pump, is also effective for treatment of hypothalamic hypogonadism when fertility is desired. In premenopausal women, cyclical replacement of estrogen and progesterone maintains secondary sexual characteristics and integ rity of genitourinary tract mucosa and prevents premature osteo porosis (Chap. 404). Gonadotropin therapy is used for ovulation induction. Follicular growth and maturation are initiated using hMG or recombinant FSH; hCG or human luteinizing hormone is subsequently injected to induce ovulation. As in men, pulsatile GnRH therapy can be used to treat hypothalamic causes of gonado tropin deficiency. ARGININE VASOPRESSIN DEFICIENCY See Chap. 393 for diagnosis and

treatment of AVP-D. ■ ■FURTHER READING Fleseriu M et al: Hormonal replacement in hypopituitarism in adults: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 101:3888, 2016. Gregory LC, Dattani MT: The molecular basis of congenital hypopi tuitarism and related disorders. J Clin Endocrinol Metab 105:e2103, 2020. Melmed S: Pathogenesis and diagnosis of growth hormone deficiency in adults. N Engl J Med 380:2551, 2019. Miller BS et al: Long-acting growth hormone preparations-current status and future considerations. J Clin Endocrinol Metab 105:e2121, 2020.

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Pituitary Tumor

Syndromes HYPOTHALAMIC, PITUITARY, AND OTHER SELLAR MASSES ■ ■EVALUATION OF SELLAR MASSES Local Mass Effects Clinical manifestations of sellar lesions vary, depending on the anatomic location of the mass and the direction of its extension (Table 392-1). The dorsal sellar diaphragm presents the least resistance to soft tissue expansion from the sella; consequently, pituitary adenomas frequently extend in a suprasellar direction. Bony invasion may occur as well, especially through the sellar floor to the sphenoid sinus (Fig. 392-1). Headaches are common features of small intrasellar tumors, even with no demonstrable suprasellar extension. Because of the confined nature of the pituitary, small changes in intrasellar pressure stretch the dural plate; however, headache severity correlates poorly with adenoma size or extension. Suprasellar extension can lead to visual loss by several mechanisms, the most common being compression of the optic chiasm. Rarely, direct invasion of the optic nerves or obstruction of cerebrospinal fluid (CSF) flow leading to secondary visual disturbances can occur. Pitu itary stalk compression by a hormonally active or inactive intrasellar mass may compress the portal vessels, disrupting pituitary access to hypothalamic hormones and dopamine; this results in early hyperpro lactinemia and later concurrent loss of other pituitary hormones. This “stalk section” phenomenon may also be caused by trauma, whiplash injury with posterior clinoid stalk compression, or skull base fractures. Lateral mass invasion may impinge on the cavernous sinus and com press its neural contents, leading to cranial nerve III, IV, and VI palsies as well as effects on the ophthalmic and maxillary branches of the fifth cranial nerve (Chap. 452). Patients may present with diplopia, ptosis, ophthalmoplegia, and decreased facial sensation, depending on the extent of neural damage. Extension into the sphenoid sinus indicates that the pituitary mass has eroded through the sellar floor (Fig. 392-1). Aggressive tumors rarely invade the palate roof and cause nasopharyn geal obstruction, infection, and CSF leakage. Temporal and frontal lobe involvement may rarely lead to uncinate seizures, personality disor ders, and anosmia. Direct hypothalamic encroachment by an invasive pituitary mass may cause important metabolic sequelae, including precocious puberty or hypogonadism, arginie vasopressin deficiency (AVP-D), sleep disturbances, dysthermia, and appetite disorders. Magnetic Resonance Imaging Sagittal and coronal T1-weighted magnetic resonance imaging (MRI) before and after administration of gadolinium allows precise visualization of the pituitary gland with

TABLE 392-1 Features of Sellar Mass Lesionsa IMPACTED STRUCTURE CLINICAL IMPACT Pituitary Hypogonadism Hypothyroidism Growth failure, adult growth hormone deficiency Hypoadrenalism Hyperprolactinema (stalk compression) Optic chiasm Loss of red perception Bitemporal hemianopia Superior or bitemporal field defect Scotoma Blindness Hypothalamus Temperature dysregulation Appetite and thirst disorders Obesity Arginine vasopression deficiency Sleep disorders Behavioral dysfunction Autonomic dysfunction Cavernous sinus Ophthalmoplegia with or without ptosis or diplopia Facial numbness Frontal lobe Personality disorder Anosmia Brain Headache Hydrocephalus Psychosis Dementia Laughing seizures aAs the intrasellar mass expands, it first compresses intrasellar pituitary tissue, then usually invades dorsally through the dura to lift the optic chiasm or laterally to the cavernous sinuses. Bony erosion is rare, as is direct brain compression. Microadenomas may present with headache. clear delineation of the hypothalamus, pituitary stalk, pituitary tissue and surrounding suprasellar cisterns, cavernous sinuses, sphenoid sinus, and optic chiasm. Pituitary gland height ranges from 6 mm in children to 8 mm in adults; during pregnancy and puberty, the height may reach 10–12 mm. The upper aspect of the adult pituitary is flat or slightly concave, but in adolescent and pregnant individuals, this sur face may be convex, reflecting physiologic pituitary enlargement. The stalk should be midline and vertical. Anterior pituitary gland soft tissue consistency is slightly hetero geneous on MRI, and signal intensity resembles that of brain matter on T1-weighted imaging (Fig. 392-2). Adenoma density is usually lower than that of surrounding normal tissue on T1-weighted imaging, and the signal intensity increases with T2-weighted images. Computed tomography (CT) scan is reserved to define the extent of bony erosion or the presence of calcification. Sellar masses are encountered commonly as incidental findings on MRI, and most are pituitary adenomas (incidentalomas). In the absence of hormone hypersecretion, these small intrasellar lesions can be monitored safely with MRI, which is performed annually and then less often if there is no evidence of further growth. Resection should be considered for incidentally discovered larger macroadenomas, because about one-third become invasive or cause local pressure effects. If hormone hypersecretion is identified, specific therapies are indicated as described below. When larger masses (>1 cm) are encountered, they should also be distinguished from nonadenomatous lesions. Meningio mas often are associated with bony hyperostosis; craniopharyngiomas may have calcifications and are usually hypodense, whereas gliomas are hyperdense on T2-weighted images. Ophthalmologic Evaluation Because optic tracts may be con tiguous to an expanding pituitary mass, reproducible visual field assessment using perimetry techniques should be performed on all patients with sellar mass lesions that impinge the optic chiasm (Chap. 34).

Bitemporal hemianopia, often more pronounced superiorly, is observed classically. It occurs because nasal ganglion cell fibers, which cross in the optic chiasm, are especially vulnerable to compression of the ventral optic chiasm. Occasionally, homonymous hemianopia occurs from postchiasmal compression or monocular temporal field loss from prechiasmal compression. Invasion of the cavernous sinus can produce diplopia from ocular motor nerve palsy. Early diagnosis reduces the risk of optic atrophy, vision loss, or eye misalignment.

Laboratory Investigation The presenting clinical features of functional pituitary adenomas (e.g., acromegaly, prolactinoma, or Cushing’s disease) should guide the laboratory studies (Table 392-2). However, for a sellar mass with no obvious clinical features of hormone excess, laboratory studies are geared toward determining the nature of the tumor and assessing the possible presence of hypopituitarism. When a pituitary adenoma is suspected based on MRI, initial hormonal evaluation

usually includes (1) basal prolactin (PRL); (2) insulin-like growth factor (IGF)-1; (3) 24-h urinary free cortisol (UFC) and/or overnight oral dexamethasone (1 mg) suppression test; (4) α subunit, follicle-stimulating hormone (FSH), and luteinizing hormone (LH); and (5) thyroid function tests. Additional hormonal evaluation may be indicated based on the results of these tests. Pending more detailed assessment of hypopituitarism, a menstrual history, measurement of testosterone and 8 A.M. cortisol levels, and thyroid function tests usu ally identify patients with pituitary hormone deficiencies that require hormone replacement before further testing or surgery (Chap. 391). Pituitary Tumor Syndromes CHAPTER 392 Histologic Evaluation Immunohistochemical staining of pitu itary tumor specimens obtained at transsphenoidal surgery for hor mones as well as cell-type specific transcription factors confirms clinical and laboratory studies and provides a histologic diagnosis when hormone studies are equivocal and in cases of clinically non functioning tumors. TREATMENT Hypothalamic, Pituitary, and Other Sellar Masses OVERVIEW Successful management of sellar masses requires accurate diagnosis as well as selection of optimal therapeutic modalities. Most pitu itary tumors are benign and slow growing. Clinical features result from local mass effects and hormonal hyper- or hyposecretion syndromes caused directly by the adenoma or occurring as a conse quence of treatment. Thus, lifelong management and follow-up are necessary for these patients. MRI with gadolinium enhancement for pituitary visualiza tion, new advances in transsphenoidal surgery and in stereotactic radiotherapy, and novel therapeutic agents have improved pitu itary tumor management. The goals of pituitary tumor treatment include normalization of excess pituitary secretion, amelioration of symptoms and signs of hormonal hypersecretion syndromes, and shrinkage or ablation of large tumor masses with relief of adjacent structure compression. Residual anterior pituitary function should be preserved during treatment and sometimes can be restored by removing the tumor mass. Ideally, adenoma recurrence should be prevented. TRANSSPHENOIDAL SURGERY Transsphenoidal resection is the desired surgical approach for pituitary tumors, except for the rare invasive suprasellar mass sur rounding the frontal or middle fossa or the optic nerves or invad ing posteriorly behind the clivus, which may require transcranial approaches. Intraoperative microscopy facilitates visual distinc tion between adenomatous and normal pituitary tissue as well as microdissection of small tumors that may not be visible by MRI (Fig. 392-3). Endoscopic techniques with three-dimensional intraoperative localization enable better visualization and access to tumor tissue. Transsphenoidal surgery also avoids cranial invasion and manipulation of brain tissue required by subfrontal surgical

 A B FIGURE 392-1 Expanding pituitary mass. Pituitary mass expansion may (A) impinge vital soft tissue structures and (B) invade the sphenoid sinus. (Reproduced with permission from P Cappabianca et al: Size does not matter. The intrigue of giant adenomas: a true surgical challenge. Acta Neurochir (Wien) 156:2217, 2014.) FIGURE 392-2 Pituitary adenoma. Coronal T1-weighted postcontrast magnetic resonance image shows a homogeneously enhancing mass (arrowheads) in the sella turcica and suprasellar region compatible with a pituitary adenoma; the small arrows outline the carotid arteries.

approaches. Individual surgical experience is a major determinant of outcome efficacy with these techniques. In addition to correction of hormonal hypersecretion, pituitary surgery is indicated for mass lesions that impinge on surround ing structures. Surgical decompression and resection are required for an expanding pituitary mass, which may be asymptomatic or accompanied by persistent headache, progressive visual field defects, cranial nerve palsies, hydrocephalus, and, occasionally, intrapituitary hemorrhage and apoplexy. Transsphenoidal surgery rarely is used for

pituitary tissue biopsy to establish a histologic diagnosis. Whenever possible, the pituitary mass lesion should be selectively excised; normal pituitary tissue should be manipulated or resected only when critical for effective mass dissection. Non selective hemihypophysectomy or total hypophysectomy may be indicated if no hypersecreting mass lesion is clearly discernible, multifocal lesions are present, or the remaining nontumorous pitu itary tissue is obviously necrotic. This strategy, however, increases the likelihood of postoperative hypopituitarism and the need for lifelong hormone replacement. Preoperative mass effects, including visual field defects and compromised pituitary function, may be reversed by surgery, par ticularly when the deficits are not long-standing. For large and invasive tumors, it is necessary to determine the optimal balance between maximal tumor resection and preservation of anterior pituitary hormonal function, especially for preserving growth and

TABLE 392-2 Screening Tests for Functional Pituitary Adenomas TEST COMMENTS Acromegaly Serum IGF-1 Oral glucose tolerance test with GH obtained at 0, 30, and 60 min Interpret IGF-1 relative to age- and sex-matched controls Normal subjects should suppress growth hormone to <1 μg/L Prolactinoma Serum PRL Exclude medications MRI of the sella should be ordered if PRL is elevated Cushing’s disease 24-h urinary free cortisol Dexamethasone (1 mg) at 11 P.M. and fasting plasma cortisol measured at 8 A.M. Late night salivary cortisol ACTH assay CRH stimulation test with measurements of cortisol and ACTH from peripheral and/or petrosal sinus blood Ensure urine collection is total and accurate Normal subjects suppress to <5 μg/dL Distinguishes adrenal adenoma (ACTH suppressed) from ectopic ACTH or Cushing’s disease (ACTH normal or elevated) The CRH test is used primarily to distinguish pituitary adenomas from ectopic ACTH sources Gonadotropinoma Baseline FSH, LH, free α subunit, ovarian hyperstimulation, estrogen (females), testosterone (males) TRH stimulation test with assays for LH, FSH, free α subunit, free LHβ, free FSHβ subunits Rare; more commonly nonfunctioning adenomas Consider screening for hypopituitarism Some gonadotropinomas exhibit an inappropriate gonadotropin response to TRH TSH-producing adenoma Free T4, free T3, TSH, free α subunit Key feature is an inappropriately normal or high TSH in the setting of elevated free T4 and T3 Abbreviations: ACTH, adrenocorticotropin hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; MRI, magnetic resonance imaging; PRL, prolactin; TSH, thyroid-stimulating hormone. reproductive function in younger patients. Tumor invasion outside the sella is rarely amenable to surgical cure, and the surgeon must judge the risk-versus-benefit ratio of extensive tumor resection. Side Effects Tumor size, the degree of invasiveness, and experi ence of the surgeon largely determine the incidence of surgical com plications. Operative mortality rate is ~1%. Transient AVP-D and hypopituitarism occur in up to 20% of patients. Permanent AVP-D, cranial nerve damage, nasal septal perforation, or visual distur bances may be encountered in up to 10% of patients. CSF leaks occur in 4% of patients. Less common complications include carotid artery injury, loss of vision, hypothalamic damage, and meningitis. Permanent side effects are rare after surgery for microadenomas. RADIATION Radiation is used either as a primary therapy for pituitary or parasellar masses or, more commonly, as an adjunct to surgery or medical therapy. Focused megavoltage irradiation is achieved by precise MRI localization, using a high-voltage linear accelerator and accurate isocentric rotational arcing. A major determinant of accu rate irradiation is reproduction of the patient’s head position during multiple visits and maintenance of absolute head immobility. A total of <50 Gy (5000 rad) is given as 180 cGy (180 rad) fractions divided over ~6 weeks. Stereotactic radiosurgery delivers a large single high-energy dose from a cobalt-60 source (Gamma

Knife), linear accelerator, or cyclotron. Long-term effects of Gamma Knife sur gery appear to be similar to those encountered with conventional radiation. Proton beam therapy is available in some centers and provides concentrated radiation doses within a localized region.

Optic chiasm Pituitary tumor Internal carotid artery Oculomotor nerve Venus plexus of cavernous sinus Trochlear nerve Trigeminal nerve Sphenoid sinus Pituitary Tumor Syndromes CHAPTER 392 Sphenoid bone Nasal septum Surgical curette Pituitary tumor Sphenoid sinus FIGURE 392-3 Transsphenoidal resection of pituitary mass via the endonasal approach. The role of radiation therapy in pituitary tumor management depends on the nature and anatomic location of the tumor, the age of the patient, and the availability of surgical and radiation exper tise. Because of its relatively slow onset of action, radiation therapy is usually reserved for postsurgical management. As an adjuvant to surgery, radiation is used to treat residual tumor in an attempt to prevent persistent growth or recurrence. Irradiation offers the only means for potentially ablating significant postoperative residual nonfunctioning tumor tissue. By contrast, PRL-, growth hormone (GH)–, adrenocorticotropin hormone (ACTH)–, and thyrotropin (thyroid-stimulating hormone [TSH])–secreting residual tumor tis sues are amenable to medical therapy. Side Effects In the short term, radiation may cause transient nau sea and weakness. Alopecia and loss of taste and smell may be more long-lasting. Failure of pituitary hormone synthesis is common in patients who have undergone head and neck or pituitary-directed irradiation. More than 50% of patients develop loss of GH, ACTH, TSH, and/or gonadotropin secretion within 10 years, usually due to hypothalamic damage. Lifelong follow-up with testing of anterior pituitary hormone reserve is therefore required after radiation treatment. Optic nerve damage with impaired vision due to optic neuritis is reported in ~2% of patients who undergo pituitary irradi ation. Cranial nerve damage is uncommon now that radiation doses are <2 Gy (200 rad) at any one treatment session and the maximum dose is <50 Gy (5000 rad). The use of stereotactic radiotherapy reduces the risk of damage to adjacent structures. Conventional

radiotherapy for pituitary tumors has been associated with adverse mortality rates, mainly from cerebrovascular disease. The cumula tive risk of developing a secondary tumor after conventional radia tion is 1.3% after 10 years and 1.9% after 20 years. MEDICAL Medical therapy for pituitary tumors is highly specific and depends on tumor type. For prolactinomas, dopamine agonists are the treatment of choice. For acromegaly, somatostatin receptor ligands (SRLs) and a GH receptor antagonist are indicated. For TSHsecreting tumors, SRLs and occasionally dopamine agonists are indicated. ACTH-secreting tumors may respond to SRLs, and adrenal-directed therapy may also be of benefit. Nonfunctioning tumors are generally not responsive to medications and require surgery and/or irradiation.

PART 12 Endocrinology and Metabolism ■ ■SELLAR MASSES Sellar masses may arise from brain, hypothalamic, or pituitary tissues. Each exhibit features related to the lesion location but also unique to the specific etiology. Unique MRI characteristics inform the differen tial diagnosis of pituitary masses (Fig. 392-4). Lesions involving the anterior and preoptic hypothalamic regions cause paradoxical vasoconstriction, tachycardia, and hyperthermia. Acute hyperthermia usually is due to a hemorrhagic insult, but poi kilothermia may also occur. Central disorders of thermoregulation result from posterior hypothalamic damage. The periodic hypothermia syndrome is characterized by episodic attacks of rectal temperatures <30°C (86°F), sweating, vasodilation, vomiting, and bradycardia (Chap. 477). Damage to the ventromedial hypothalamic nuclei by cra

niopharyngiomas, hypothalamic trauma, or inflammatory disorders may be associated with hyperphagia and obesity. This region appears to contain an energy-satiety center where melanocortin receptors are influenced by leptin, insulin, pro-opiomelanocortin (POMC) products, and gastrointestinal peptides (Chap. 413). Polydipsia and hypodipsia are associated with damage to central osmoreceptors located in preoptic nuclei (Chap. 393). Slow-growing hypothalamic lesions can cause increased somnolence and disturbed sleep cycles as well as obesity, hypothermia, and emotional outbursts. Lesions of the central hypothalamus may stimulate sympathetic neurons, leading to A B C FIGURE 392-4 Imaging differential diagnosis of sellar masses. A. Microadenoma. B. Macroadenoma. C. Craniopharyngioma. D. Hypophysitis with stalk thickening. (A, B, D: Used with permission from Vivien Bonert, MD. C: Reproduced with permission from Muller HL: Childhood craniopharyngioma. Recent advances in diagnosis, treatment and follow-up. Horm Res 69:193, 2008.)

elevated serum catecholamine and cortisol levels. These patients are predisposed to cardiac arrhythmias, hypertension, and gastric erosions. Craniopharyngiomas are benign, suprasellar cystic masses that present with headaches, visual field deficits, and variable degrees of hypopituitarism. They are derived from Rathke’s pouch and arise near the pituitary stalk, commonly extending into the suprasellar cistern. Craniopharyngiomas are often large, cystic, and locally invasive. Many are partially calcified, exhibiting a characteristic appearance on skull x-ray and CT images. More than half of all patients present before age 20, usually with signs of increased intracranial pressure, includ ing headache, vomiting, papilledema, and hydrocephalus. Associated symptoms include visual field abnormalities, personality changes and cognitive deterioration, cranial nerve damage, sleep difficulties, and weight gain accompanied by features of the metabolic syndrome. Hypopituitarism is documented in ~90%, and AVP-D occurs in ~10% of patients. About half of affected children present with growth retar dation. MRI is generally superior to CT for evaluating cystic structure and tissue components of craniopharyngiomas. CT is useful to define calcifications and evaluate invasion into surrounding bony structures and sinuses. Treatment usually involves transcranial or transsphenoidal surgi cal resection followed by postoperative radiation of residual tumor. Surgery alone is curative in less than half of patients because of recur rences due to adherence to vital structures or because of small tumor deposits in the hypothalamus or brain parenchyma. The goal of surgery is to remove as much tumor as possible without risking complications associated with efforts to remove firmly adherent or inaccessible tissue. In the absence of radiotherapy, ~75% of craniopharyngiomas recur, and 10-year survival is <50%. In patients with incomplete resection, radiotherapy improves 10-year survival to 70–90% but is associated with increased risk of secondary malignancies. Most patients require lifelong pituitary hormone replacement. As some craniopharyngiomas (particularly papillary) are associated with activated BRAF V600E mutations, use of BRAF inhibitors (dabrafenib or vemurafenib) either alone or in combination with MEK inhibitors (trametinib or cobi metinib) has resulted in long-term growth responses in some patients. Developmental failure of Rathke’s pouch obliteration may lead to Rathke’s cysts, which are small (<5 mm) cysts entrapped by squamous epithelium and are found in ~20% of individuals at autopsy. Although D

Rathke’s cysts do not usually grow and are often diagnosed inciden tally, about a third present in adulthood with compressive symptoms, AVP-D, and hyperprolactinemia due to stalk compression. Rarely, hydrocephalus develops. The diagnosis is suggested preoperatively by visualizing the cyst wall on MRI, which distinguishes these lesions from craniopharyngiomas. Cyst contents range from

CSF-like fluid to mucoid material. Arachnoid cysts are rare and generate an MRI image that is isointense with CSF. Sellar chordomas usually present with bony clival erosion, local invasiveness, and, on occasion, calcification. Normal pituitary tissue may be visible on MRI, distinguishing chordomas from aggressive pitu itary adenomas. Mucinous material may be obtained by fine-needle aspiration. Meningiomas arising in the sellar region may be difficult to distin guish from nonfunctioning pituitary adenomas. Meningiomas typi cally enhance on MRI and may show evidence of calcification or bony erosion. Meningiomas may cause compressive symptoms. Histiocytosis X includes a variety of syndromes associated with foci of eosinophilic granulomas. AVP-D, exophthalmos, and punched-out lytic bone lesions (Hand-Schüller-Christian disease) are associated with granulomatous lesions visible on MRI, as well as a characteristic axil lary skin rash. Rarely, the pituitary stalk may be involved. Pituitary metastases occur in ~3% of cancer patients. Bloodborne metastatic deposits are found almost exclusively in the posterior pitu itary. Accordingly, AVP-D can be a presenting feature of lung, gastro intestinal, breast, and other pituitary metastases. About half of pituitary metastases originate from breast cancer; ~25% of patients with meta static breast cancer have such deposits. Rarely, pituitary stalk involve ment results in anterior pituitary insufficiency. The MRI diagnosis of a metastatic lesion may be difficult to distinguish from an aggressive pituitary adenoma; the diagnosis may require histologic examination of excised tumor tissue. Primary or metastatic lymphoma, leukemias, and plasmacytomas also occur within the sella. Hypothalamic hamartomas and gangliocytomas may arise from astrocytes, oligodendrocytes, and neurons with varying degrees of differentiation. These tumors may overexpress hypothalamic neuro peptides, including gonadotropin-releasing hormone (GnRH), growth hormone–releasing hormone (GHRH), and corticotropin-releasing hormone (CRH). With GnRH-producing tumors, children present with precocious puberty, psychomotor delay, and laughing-associated seizures. Medical treatment of GnRH-producing hamartomas with long-acting GnRH analogues effectively suppresses gonadotropin secretion and controls premature pubertal development. Rarely, ham artomas also are associated with craniofacial abnormalities; imperfo rate anus; cardiac, renal, and lung disorders; and pituitary failure as features of Pallister-Hall syndrome, which is caused by mutations in the carboxy terminus of the GLI3 gene. Hypothalamic hamartomas are often contiguous with the pituitary, and preoperative MRI diagnosis may not be possible. Histologic evidence of hypothalamic neurons in tissue resected at transsphenoidal surgery may be the first indication of a primary hypothalamic lesion. Hypothalamic gliomas and optic gliomas occur mainly in childhood and usually present with visual loss. Adults have more aggressive tumors; about a third are associated with neurofibromatosis. Brain germ cell tumors may arise within the sellar region. They include dysgerminomas, which frequently are associated with AVP-D and visual loss. They rarely metastasize. Germinomas, embryonal car cinomas, teratomas, and choriocarcinomas may arise in the parasellar region and produce human chorionic gonadotropin (hCG). These germ cell tumors present with precocious puberty, AVP-D, visual field defects, and thirst disorders. Many patients are GH deficient with short stature. ■ ■PITUITARY ADENOMAS AND HYPERSECRETION SYNDROMES Pituitary adenomas are the most common cause of pituitary hormone hypersecretion and hyposecretion syndromes in adults. They account for ~15% of all intracranial neoplasms and have been identified with a population prevalence of ~80/100,000. At autopsy, up to one-quarter

of all pituitary glands harbor an unsuspected microadenoma (<10 mm diameter). Similarly, pituitary imaging detects small clinically inappar ent pituitary lesions in at least 10% of individuals.

Pathogenesis Pituitary adenomas are benign neoplasms that arise from one of the five anterior pituitary cell types. The clinical and bio chemical phenotypes of pituitary adenomas depend on the cell type from which they are derived. Thus, tumors arising from lactotrope (PRL), somatotrope (GH), corticotrope (ACTH), thyrotrope (TSH), or gonadotrope (LH, FSH) cells hypersecrete their respective hormones (Table 392-3). Plurihormonal tumors express various combinations of GH, PRL, TSH, ACTH, or the glycoprotein hormone α or β subunits. They may be diagnosed by careful immunocytochemistry of specific hormone and transcription factor expression or may manifest as clini cal syndromes that combine features of these hormonal hypersecretory syndromes. Morphologically, these tumors may arise from a single polysecreting cell type or include cells with mixed function within the same tumor. Pituitary Tumor Syndromes CHAPTER 392 Hormonally active tumors are characterized by autonomous hor mone secretion with diminished feedback responsiveness to physi ologic inhibitory pathways. Hormone production does not always correlate with tumor size. Small hormone-secreting adenomas may cause significant clinical perturbations, whereas larger adenomas that produce less hormone may be clinically silent and remain undiagnosed (if no central compressive effects occur). About one-third of all adeno mas are clinically nonfunctioning and produce no distinct clinical hypersecretory syndrome. Most of them arise from gonadotrope cells and may secrete small amounts of α- and β-glycoprotein hormone subunits or, very rarely, intact circulating gonadotropins. True pituitary carcinomas with documented extracranial metastases are exceedingly rare. Almost all pituitary adenomas are monoclonal in origin, implying the acquisition of one or more somatic mutations that confer a selec tive growth advantage. Consistent with their clonal origin, complete surgical resection of small pituitary adenomas usually cures hormone hypersecretion. Nevertheless, hypothalamic hormones such as GHRH and CRH also enhance mitotic activity of their respective pituitary tar get cells in addition to their role in pituitary hormone regulation. Thus, patients who harbor rare abdominal or chest tumors that produce ectopic GHRH or CRH may present with somatotrope or corticotrope hyperplasia with GH or ACTH hypersecretion. TABLE 392-3 Classification of Pituitary Adenomasa HORMONE PRODUCT CLINICAL SYNDROME ADENOMA CELL ORIGIN Lactotrope PRL Hypogonadism, galactorrhea Gonadotrope FSH, LH, subunits Silent/nonfunctioning, ovarian hyperstimulation, hypogonadism Somatotrope GH Acromegaly/gigantism Corticotrope ACTH/none Cushing’s disease or silent Mixed lactotrope and somatotrope GH, PRL Acromegaly, hypogonadism, galactorrhea Other plurihormonal cell Any Mixed Acidophil stem cell PRL, GH Hypogonadism, galactorrhea, acromegaly Mammosomatotrope PRL, GH Hypogonadism, galactorrhea, acromegaly Thyrotrope TSH Thyrotoxicosis Null cell None Hypopituitarism/none Oncocytoma None Hypopituitarism/none aHormone-secreting tumors are listed in decreasing order of frequency. All tumors may cause local pressure effects, including visual disturbances, cranial nerve palsy, and headache. Note: For abbreviations, see text. Source: Reproduced with permission from S Melmed: Pathogenesis of pituitary tumors. Nat Rev Endocrinol 7:257, 2011.

Several etiologic genetic events have been implicated in the develop ment of pituitary tumors. The pathogenesis of sporadic forms of acro megaly has been particularly informative as a model of tumorigenesis. GHRH, after binding to its G protein–coupled somatotrope receptor, uses cyclic adenosine monophosphate (AMP) as a second messenger to stimulate GH secretion and somatotrope proliferation. A subset (~35%) of GH-secreting pituitary tumors contains sporadic mutations in Gsα. These mutations attenuate intrinsic GTPase activity, resulting in constitutive elevation of cyclic AMP, Pit-1 induction, and activation of cyclic AMP response element binding protein (CREB), thereby pro moting somatotrope cell proliferation and GH secretion.

Growth factors may also promote pituitary tumor proliferation. Basic fibroblast growth factor (bFGF) is abundant in the pituitary and stimulates pituitary cell mitogenesis, whereas epidermal growth factor receptor (EGFR) signaling induces both hormone synthesis and cell proliferation. Mutations of USP8 may result in overexpressed EGFR in a subset of ACTH-secreting tumors. Other factors involved in initiation and promotion of pituitary tumors include loss of negativefeedback inhibition (as seen with primary hypothyroidism or hypo gonadism) and estrogen-mediated or paracrine angiogenesis. Growth characteristics and neoplastic behavior also may be influenced by activated oncogenes, including RAS and pituitary tumor transforming gene (PTTG), or inactivation of growth suppressor genes, including MEG3. Pituitary adenomas exhibit lineage-specific features of cellcycle disruption, including cellular senescence, with chromosomal instability and copy number alterations as well as elevated levels of CDK inhibitors. These features underlie the invariably benign nature of these adenomas. PART 12 Endocrinology and Metabolism Genetic Syndromes Associated with Pituitary Tumors Several familial syndromes are associated with pituitary tumors, and the genetic mechanisms for some of them have been unraveled (Table 392-4). Multiple endocrine neoplasia (MEN) 1 is an autosomal dominant syndrome characterized primarily by a genetic predisposition to para thyroid, pancreatic islet, and pituitary adenomas (Chap. 400). MEN 1 is caused by inactivating germline mutations in MENIN, a consti tutively expressed tumor-suppressor gene located on chromosome 11q13. Loss of heterozygosity or a somatic mutation of the remaining normal MENIN allele leads to tumorigenesis. About half of affected patients develop prolactinomas; acromegaly and Cushing’s disease are less commonly encountered. Carney complex is characterized by spotty skin pigmentation, myxo mas, and endocrine tumors, including testicular, adrenal, and pituitary adenomas. Acromegaly occurs in ~20% of these patients. A subset of patients has mutations in the R1α regulatory subunit of protein kinase A (PRKAR1A). TABLE 392-4 Familial Pituitary Tumor Syndromes (See Chap. 400) GENE MUTATED CLINICAL FEATURES Multiple endocrine neoplasia 1 (MEN 1) MEN1 (11q13) Hyperparathyroidism Pancreatic neuroendocrine tumors Foregut carcinoids Adrenal adenomas Skin lesions Pituitary adenomas (40%) Multiple endocrine neoplasia 4 (MEN 4) CDKNIB (12p13) Hyperparathyroidism Pituitary adenomas Other tumors Carney complex PRKAR1A (17q23-24) Pituitary hyperplasia and adenomas (10%) Atrial myxomas Schwannomas Adrenal hyperplasia Lentigines Familial pituitary adenomas AIP (11q13.2) Acromegaly/gigantism (~15% of afflicted families)

McCune-Albright syndrome consists of polyostotic fibrous dysplasia, pigmented skin patches, and a variety of endocrine disorders, includ ing acromegaly, adrenal adenomas, and autonomous ovarian function (Chap. 424). Hormonal hypersecretion results from constitutive cyclic AMP production caused by inactivation of the GTPase activity of Gsα. The Gsα mutations occur postzygotically, leading to a mosaic pattern of mutant expression. Familial acromegaly is a rare disorder in which family members may manifest either acromegaly or gigantism. A subset of families with a predisposition for familial pituitary tumors, especially acromegaly, has been found to harbor germline mutations in the AIP gene, which encodes the aryl hydrocarbon receptor interacting protein. ■ ■HYPERPROLACTINEMIA Etiology Hyperprolactinemia is the most common pituitary hor mone hypersecretion syndrome in both men and women. PRL-secret ing pituitary adenomas (prolactinomas) are the most common cause of PRL levels >200 μg/L (see below). Less pronounced PRL elevation can also be seen with microprolactinomas but is more commonly caused by drugs, pituitary stalk compression, hypothyroidism, or renal failure (Table 392-5). Pregnancy and lactation are the important physiologic causes of hyperprolactinemia. Sleep-associated hyperprolactinemia reverts to normal within an hour of awakening. Nipple stimulation and sexual orgasm also may

increase PRL. Chest wall stimulation or trauma (including chest surgery and herpes zoster) invokes the reflex suckling arc with resultant hyperprolactinemia. Chronic renal failure elevates PRL by decreasing peripheral clearance. Primary hypothyroidism is associated with mild hyperprolactinemia, probably because of com pensatory TRH secretion. Mutation of the PRL receptor is a rare cause of hyperprolactinemia. Lesions of the hypothalamic-pituitary region that disrupt hypo thalamic dopamine synthesis, portal vessel delivery, or lactotrope responses are associated with hyperprolactinemia. Thus, hypothalamic tumors, cysts, infiltrative disorders, and radiation-induced dam age cause elevated PRL levels, usually in the range of 30–100 µg/L. Plurihormonal adenomas (including GH and ACTH tumors) may hypersecrete PRL directly. Pituitary masses, including clinically non functioning pituitary tumors, may compress the pituitary stalk to cause hyperprolactinemia. Drug-induced inhibition or disruption of dopaminergic receptor function is a common cause of hyperprolactinemia (Table 392-5). Thus, antipsychotics and antidepressants are a relatively common cause of mild hyperprolactinemia. Most patients receiving risperidone have elevated PRL levels, sometimes exceeding 200 µg/L. Methyldopa inhibits dopamine synthesis, and verapamil blocks dopamine release, also leading to hyperprolactinemia. Hormonal agents that induce PRL include estrogens and thyrotropin-releasing hormone (TRH). Presentation and Diagnosis Amenorrhea, galactorrhea, and infertility are the hallmarks of hyperprolactinemia in women. If hyper prolactinemia develops before menarche, primary amenorrhea results. More commonly, hyperprolactinemia develops later in life and leads to oligomenorrhea and ultimately to amenorrhea. If hyperprolactinemia is sustained, vertebral bone mineral density can be reduced compared with age-matched controls, particularly when it is associated with pro nounced hypoestrogenemia. Galactorrhea is present in up to 80% of hyperprolactinemic women. Although usually bilateral and spontane ous, it may be unilateral or expressed only manually. Patients also may complain of decreased libido, weight gain, and mild hirsutism. In men with hyperprolactinemia, diminished libido, infertility, and visual loss (from optic nerve compression) are the usual presenting symptoms. Gonadotropin suppression leads to reduced testosterone, impotence, and oligospermia. True galactorrhea is uncommon in men with hyperprolactinemia. If the disorder is long-standing, secondary effects of hypogonadism are evident, including osteopenia, reduced muscle mass, and decreased beard growth. The diagnosis of idiopathic hyperprolactinemia is made by exclu sion of known causes of hyperprolactinemia in the setting of a normal

TABLE 392-5 Etiology of Hyperprolactinemia I. Physiologic hypersecretion Pregnancy Lactation Chest wall stimulation Sleep Stress II. Hypothalamic-pituitary stalk damage Pituitary adenoma with stalk compression Suprasellar mass Craniopharyngioma Meningioma Dysgerminoma Metastases Empty sella Lymphocytic hypophysitis Granulomas Rathke’s cyst Irradiation Trauma Pituitary stalk section Suprasellar surgery III. Pituitary adenoma hypersecretion Prolactinoma Acromegaly IV. Systemic disorders Chronic renal failure Hypothyroidism Cirrhosis Pseudocyesis Epileptic seizures V. Drug-induced hypersecretion Dopamine receptor blockers Atypical antipsychotics: risperidone Phenothiazines: chlorpromazine, perphenazine Butyrophenones: haloperidol Thioxanthenes Metoclopramide Dopamine synthesis inhibitors α-Methyldopa Catecholamine depletors Reserpine Opiates H2 antagonists Cimetidine, ranitidine Imipramines Amitriptyline, amoxapine Serotonin reuptake inhibitors Fluoxetine Calcium channel blockers Verapamil Estrogens Thyrotropin-releasing hormone Note: Hyperprolactinemia >200 µg/L almost invariably is indicative of a prolactinsecreting pituitary adenoma. Physiologic causes, hypothyroidism, and drug-induced hyperprolactinemia should be excluded before extensive evaluation. pituitary MRI. Some of these patients may harbor

small microadeno mas below visible MRI sensitivity (~2 mm). ■ ■GALACTORRHEA Galactorrhea, the inappropriate discharge of milk-containing fluid from the breast, is considered abnormal if it persists longer than 6 months after childbirth or discontinuation of breast-feeding. Postpartum

galactorrhea associated with amenorrhea is a self-limiting disorder usually associated with moderately elevated PRL levels. Galactorrhea may occur spontaneously, or it may be elicited by nipple pressure. In both men and women, galactorrhea may vary in color and consistency (transparent, milky, or bloody) and arise either unilaterally or bilater ally. Mammography or ultrasound is indicated for bloody discharges (particularly from a single nipple), which may be caused by breast cancer. Galactorrhea is commonly associated with hyperprolactinemia caused by any of the conditions listed in Table 392-5. Acromegaly is associated with galactorrhea in about one-third of patients. Treatment of galactorrhea usually involves managing the underlying disorder (e.g., replacing T4 for hypothyroidism, discontinuing a medication, treating prolactinoma).

Pituitary Tumor Syndromes CHAPTER 392 Laboratory Investigation Basal, fasting morning PRL levels (normally <20 µg/L) should be measured to assess hypersecretion. Both false-positive and false-negative results may be encountered. In patients with markedly elevated PRL levels (>1000 µg/L), reported results may be falsely lowered because of assay artifacts; sample dilution is required to measure these high values accurately. Falsely elevated values may be caused by aggregated forms of circulating PRL, which are usually biologically inactive (macroprolactinemia). Hypo thyroidism should be excluded by measuring TSH and T4 levels. TREATMENT Hyperprolactinemia Treatment of hyperprolactinemia depends on the cause of elevated PRL levels. Regardless of the etiology, however, treatment should be aimed at normalizing PRL levels to alleviate suppressive effects on gonadal function, halt galactorrhea, and preserve bone mineral density. Dopamine agonists are effective for most causes of hyper prolactinemia (see the treatment section for prolactinoma, below) regardless of the underlying cause. If the patient is taking a medication known to cause hyperprolac tinemia, the drug should be withdrawn, if possible. For psychiatric patients who require neuroleptic agents, supervised dose titration or the addition of a dopamine agonist can help restore normopro lactinemia and alleviate reproductive symptoms. However, dopa mine agonists may worsen the underlying psychiatric condition, especially at high doses. Hyperprolactinemia usually resolves after adequate thyroid hormone replacement in hypothyroid patients or after renal transplantation in patients undergoing dialysis. Resec tion of hypothalamic or sellar mass lesions can reverse hyperprolac tinemia caused by stalk compression and reduced dopamine tone. Granulomatous infiltrates occasionally respond to glucocorticoid administration. In patients with irreversible hypothalamic dam age, no treatment may be warranted. In up to 30% of patients with hyperprolactinemia—usually without a visible pituitary microad enoma—the condition may resolve spontaneously. ■ ■PROLACTINOMA Etiology and Prevalence Tumors arising from lactotropes account for about half of all functioning pituitary tumors, with a popu lation prevalence of ~10/100,000 in men and ~30/100,000 in women. Mixed tumors that secrete combinations of GH and PRL, ACTH and PRL, and rarely TSH and PRL are also seen. These plurihormonal tumors are usually recognized by immunohistochemistry, sometimes without apparent clinical manifestations from the production of addi tional hormones. Microadenomas are classified as <1 cm in diameter and usually do not invade the parasellar region. Macroadenomas are ≥1 cm in diameter and may be locally invasive and impinge on adjacent structures. The female-to-male ratio for microprolactinomas is 20:1, whereas the sex ratio is near 1:1 for macroadenomas. Tumor size generally correlates directly with PRL concentrations;

values

> 250 µg/L usually are associated with macroadenomas. Men tend to present with larger tumors than women, possibly because the features of male hypogonadism are less readily evident. PRL levels remain stable

in most patients, reflecting the slow growth of these tumors. About 5% of microadenomas progress in the long term to macroadenomas.

Presentation and Diagnosis Women usually present with amen orrhea, infertility, and galactorrhea. If the tumor extends outside the sella, visual field defects or other mass effects may be seen. Men often present with impotence, loss of libido, infertility, or signs of central nervous system (CNS) compression, including headaches and visual defects. Assuming that physiologic and medication-induced causes of hyperprolactinemia are excluded (Table 392-5), the diagnosis of pro lactinoma is likely with a PRL level >200 µg/L. PRL levels <100 µg/L may be caused by microadenomas, other sellar lesions that decrease dopamine inhibition, or nonneoplastic causes of hyperprolactinemia. For this reason, an MRI should be performed in all patients with hyperprolactinemia. It is important to remember that hyperprolac tinemia caused secondarily by the mass effects of nonlactotrope lesions is also corrected by treatment with dopamine agonists despite failure to shrink the underlying mass. Consequently, PRL suppression by dopa mine agonists does not necessarily indicate that the underlying lesion is a prolactinoma. PART 12 Endocrinology and Metabolism TREATMENT Prolactinoma Because microadenomas rarely progress to become macroadeno mas, no treatment may be needed if patients are asymptomatic and fertility is not desired; these patients should be monitored by regular serial PRL measurements and MRI scans. For symptomatic microadenomas, therapeutic goals include control of hyperprolac tinemia, reduction of tumor size, restoration of menses and fertility, and resolution of galactorrhea. Dopamine agonist doses should be titrated to achieve maximal PRL suppression and restoration of reproductive function (Fig. 392-5). A normalized PRL level does not ensure reduced tumor size. However, tumor shrinkage usually is not seen in those who do not respond with lowered PRL levels. For macroadenomas, formal visual field testing should be performed before initiating dopamine agonists. MRI and visual fields should be assessed at 6- to 12-month intervals until the mass shrinks and annually thereafter until maximum size reduction has occurred. ELEVATED PROLACTIN LEVELS Exclude secondary causes of hyperprolactinemia MRI evidence for pituitary mass Symptomatic Prolactinoma Microadenoma Macroadenoma Titrate dopamine agonist Drug intolerance Titrate dopamine agonist Change dopamine agonist Serum PRL <20

> 50 (µg/L) 20–50 Maintenance Rx Consider Surgery Reassess diagnosis Increase dose FIGURE 392-5 Management of prolactinoma. MRI, magnetic resonance imaging; PRL, prolactin.

Oral dopamine agonists (cabergoline and bromocriptine) are the mainstay of therapy for patients with micro- or macroprolactinomas. Dopamine agonists suppress PRL secretion and synthesis as

well as lactotrope proliferation. In patients with microadenomas who have achieved normoprolactinemia and significant reduction of tumor mass, the dopamine agonist may be withdrawn after 2 years. These patients should be monitored carefully for evidence of prolactinoma recurrence. About 20% of patients (especially males) are resistant to dopaminergic treatment; these adenomas may exhibit decreased D2 dopamine receptor numbers or a postreceptor defect. D2 receptor gene mutations in the pituitary have not been reported. Cabergoline An ergoline derivative, cabergoline is a long-acting dopamine agonist with high D2 receptor affinity. The drug effectively suppresses PRL for >14 days after a single oral dose and induces prolactinoma shrinkage in most patients. Cabergoline (0.5–1.0 mg twice weekly) achieves normoprolactinemia and resumption of normal gonadal function in ~80% of patients with microadenomas; galactorrhea improves or resolves in 90% of patients. Cabergoline normalizes PRL and shrinks ~70% of macroprolactinomas. Mass effect symptoms, including headaches and visual disorders, usu ally improve dramatically within days after cabergoline initiation; improvement of sexual function requires several weeks of treat ment but may occur before complete normalization of PRL levels. MRI should be repeated within 16 weeks after initial therapy of macroadenomas as shrinkage of invasive adenomas may be striking (Fig. 392-6). After initial control of PRL levels has been achieved, cabergoline should be reduced to the lowest effective maintenance dose. In ~5% of treated patients harboring a microadenoma, hyper prolactinemia may resolve and not recur when dopamine agonists are discontinued after long-term treatment. Cabergoline also may be effective in patients resistant to bromocriptine. Adverse effects and drug intolerance are encountered less commonly than with bromocriptine. Bromocriptine The ergot alkaloid bromocriptine mesylate is a dopamine receptor agonist that suppresses PRL secretion. Because it is short-acting, the drug is preferred when pregnancy is desired. Therapy is initiated by administering a low bromocriptine dose (0.625–1.25 mg) at bedtime with a snack, followed by gradually Test visual fields Test pituitary reserve function Repeat MRI within 4 months Tumor shrinkage and prolactin normalized No tumor shrinkage or tumor growth or persistent hyperprolactinemia Monitor PRL and repeat MRI annually

A B C D FIGURE 392-6 Large invasive prolactinoma successfully treated with cabergoline. A–B. Prolactin-secreting macroadenoma in a 32-year-old male measuring 5.6 × 6.9 cm invading the skull base. PRL level was 122,260 µg/L. Four days after cabergoline was started, PRL was 10,823 µg/L and dropped to 772 µg/L after 3 weeks. C–D. Substantial tumor regression after 40 months of treatment, with PRL levels stable at 25 µg/L. (Reproduced with permission from M Ahmed, O Al-Nozha: Images in clinical medicine. Large prolactinoma. N Engl J Med 363:177, 2010.) increasing the dose. Most patients are controlled with a daily dose of <7.5 mg (2.5 mg tid). SIDE EFFECTS Side effects of dopamine agonists include constipation, nasal stuffi ness, dry mouth, nightmares, insomnia, and vertigo; decreasing the dose usually alleviates these problems. Nausea, vomiting, and postural hypotension with faintness may occur in ~25% of patients after the initial dose. These symptoms may persist in some patients. In general, fewer side effects are reported with cabergoline. For the ~15% of patients who are intolerant of oral bromocriptine, cabergoline may be better tolerated. Intravaginal administration of bromocriptine is often efficacious in patients with intractable gastrointestinal side effects. Auditory hallucinations, delusions, mood swings, and impulse control disorders have been reported in up to 5% of patients and may be due to the dopamine agonist properties or to the lysergic acid derivative of the compounds. Rare reports of leukopenia, thrombocytopenia, pleural fibrosis, car diac arrhythmias, and hepatitis have been described. Patients with Parkinson disease who receive at least 3 mg of cabergoline daily have

been reported to be at risk for development of cardiac valve

Pituitary Tumor Syndromes CHAPTER 392 regurgitation. Studies analyzing >500 prolactinoma patients receiv ing recommended doses of cabergoline (up to 2 mg weekly) have shown no evidence for an increased incidence of valvular disorders. Nevertheless, because no controlled prospective studies in pituitary tumor patients are available, it is prudent to perform echocardio grams before initiating standard-dose cabergoline therapy. Surgery Surgical adenoma debulking may be indicated for dopa mine resistance or intolerance as well as the presence of an invasive macroadenoma with compromised vision that fails to improve after drug treatment. Initial PRL normalization is achieved in ~70% of microprolactinomas after surgical resection, but only 40% of mac roadenomas can be resected successfully. Follow-up studies have shown that hyperprolactinemia recurs in up to 20% of patients within the first year after surgery; long-term recurrence rates may exceed 50% for macroadenomas. Radiotherapy for prolactinomas is reserved for patients with aggressive tumors that do not respond to maximally tolerated dopamine agonists and/or surgery. PREGNANCY The pituitary increases in size during pregnancy, reflecting the stimulatory effects of estrogen and perhaps other growth factors

on pituitary vascularity and lactotrope hyperplasia. About 5% of microadenomas significantly increase in size, but 15–30% of macroadenomas grow during pregnancy. Bromocriptine has been used for >30 years to restore fertility in women with hyperprolac tinemia, without evidence of teratogenic effects. Nonetheless, most authorities recommend strategies to minimize fetal exposure to the drug. For women taking bromocriptine who desire pregnancy, mechanical contraception should be used through three regular menstrual cycles to allow for conception timing. When pregnancy is confirmed, bromocriptine should be discontinued and PRL levels followed serially, especially if headaches or visual symptoms occur. For women harboring macroadenomas, regular visual field test ing is recommended, and the drug should be reinstituted if tumor growth is apparent. Although pituitary MRI may be safe during pregnancy, this procedure should be reserved for symptomatic patients with severe headache and/or visual field defects. Surgical decompression may be indicated if vision is threatened. Although comprehensive data support the efficacy and relative safety of bromocriptine-facilitated fertility, patients should be advised of potential unknown deleterious effects and the risk of tumor growth during pregnancy. Because cabergoline is long-acting with a high D2-receptor affinity, it is not recommended for use in women when fertility is desired.

PART 12 Endocrinology and Metabolism ■ ■ACROMEGALY Etiology GH hypersecretion is usually the result of a somato trope adenoma but may rarely be caused by extrapituitary lesions (Table 392-6). In addition to the more common GH-secreting somato trope adenomas, mixed mammosomatotrope tumors and acidophilic stem cell adenomas secrete both GH and PRL. In patients with acido philic stem cell adenomas, features of hyperprolactinemia (hypogo nadism and galactorrhea) predominate over the less clinically evident signs of acromegaly. Occasionally, mixed plurihormonal tumors are encountered that also secrete ACTH, the glycoprotein hormone α subunit, or TSH in addition to GH. Patients with partially empty sel lae may present with GH hypersecretion due to a small GH-secreting adenoma within the compressed rim of pituitary tissue; some of these may reflect the spontaneous necrosis of tumors that were previously TABLE 392-6 Causes of Acromegaly PREVALENCE, % Excess Growth Hormone Secretion Pituitary Densely or sparsely granulated GH cell adenoma Mixed GH cell and PRL cell adenoma Mammosomatotrope

cell adenoma Plurihormonal adenoma GH cell carcinoma or metastases Multiple endocrine neoplasia 1 (GH cell adenoma) McCune-Albright syndrome Ectopic sphenoid or parapharyngeal sinus pituitary

adenoma Extrapituitary tumor Pancreatic islet cell tumor Lymphoma <1 Excess Growth Hormone–Releasing Hormone Secretion Central Hypothalamic hamartoma, choristoma, ganglioneuroma Peripheral Bronchial carcinoid, pancreatic islet cell tumor, small- <1 <1 cell lung cancer, adrenal adenoma, medullary thyroid carcinoma, pheochromocytoma Abbreviations: GH, growth hormone; PRL, prolactin. Source: Data from S Melmed: Medical progress: Acromegaly. N Engl J Med 355:2558, 2006.

larger. GH-secreting tumors rarely arise from ectopic pituitary tissue remnants in the nasopharynx or midline sinuses. There are case reports of ectopic GH secretion by tumors of pan creatic, ovarian, lung, or hematopoietic origin. Rarely, excess GHRH production may cause acromegaly because of chronic stimulation of somatotropes. These patients present with classic features of acromeg aly, elevated GH levels, pituitary enlargement on MRI, and pathologic characteristics of pituitary hyperplasia. The most common cause of GHRH-mediated acromegaly is a chest or abdominal carcinoid tumor. Although these tumors usually express positive GHRH immunoreac tivity, clinical features of acromegaly are evident in only a minority of patients with carcinoid disease. Excessive GHRH also may be elabo rated by hypothalamic tumors, usually choristomas or neuromas. Presentation and Diagnosis Protean manifestations of GH and IGF-1 hypersecretion are indolent and often are not clinically diag nosed for 10 years or more. Acral bony overgrowth results in frontal bossing, increased hand and foot size, mandibular enlargement with prognathism, and widened space between the lower incisor teeth. In children and adolescents, initiation of GH hypersecretion before epiphyseal long bone closure is associated with development of pitu itary gigantism (Fig. 392-7). Soft tissue swelling results in increased heel pad thickness, increased shoe or glove size, ring tightening, characteristic coarse facial features, and a large fleshy nose. Other commonly encountered clinical features include hyperhidrosis, a deep and hollow-sounding voice, oily skin, arthropathy, kyphosis, carpal tunnel syndrome, proximal muscle weakness and fatigue, acanthosis nigricans, and skin tags. Generalized visceromegaly occurs, including cardiomegaly, macroglossia, and thyroid gland enlargement. The most significant clinical impact of GH excess occurs with respect to the cardiovascular system. Cardiomyopathy with arrhyth mias, left ventricular hypertrophy, decreased diastolic function, and hypertension ultimately occur in most patients if untreated. Upper airway obstruction with sleep apnea occurs in >60% of patients and is associated with both soft tissue laryngeal airway obstruction and central sleep dysfunction. Diabetes mellitus develops in 25% of patients with acromegaly, and most patients are intolerant of a glucose load (as GH counteracts the action of insulin). Acromegaly is associated with an increased risk of colon polyps and mortality from colonic malig nancy; polyps are diagnosed in up to one-third of patients. Overall mortality is increased about threefold and is due primarily to cardio vascular and cerebrovascular disorders and respiratory disease. Unless GH levels are controlled, survival is reduced by an average of 10 years compared with an age-matched control population. Laboratory Investigation Age-matched serum IGF-1 levels are elevated in acromegaly. Consequently, an IGF-1 level provides a use ful laboratory screening measure when clinical features raise the possibility of acromegaly. Owing to the pulsatility of GH secretion, measurement of a single random GH level is not useful for the diag nosis or exclusion of acromegaly and does not correlate with disease severity. The diagnosis of acromegaly is confirmed by demonstrating the

failure of GH suppression to <0.4 µg/L within 1–2 h of an oral glucose load (75 g). When ultrasensitive GH assays are used, normal nadir GH levels are even lower (<0.05 µg/L). About 20% of patients exhibit a paradoxical GH rise after glucose. PRL should be measured, as it is elevated in ~25% of patients with acromegaly. Thyroid function, gonadotropins, and sex steroids may be attenuated because of tumor mass effects. Because most patients will undergo surgery with gluco corticoid coverage, tests of ACTH reserve in asymptomatic patients are more efficiently deferred until after surgery. TREATMENT Acromegaly The goal of treatment is to control GH and IGF-1 hypersecretion, ablate or arrest tumor growth, ameliorate comorbidities, restore mortality rates to normal, and preserve pituitary function. Surgical resection of GH-secreting adenomas is the initial treat ment for most patients (Fig. 392-8). SRLs are used as adjuvant

A FIGURE 392-7 Features of acromegaly/gigantism. A 22-year-old man with gigantism due to excess growth hormone is shown to the left of his identical twin. The increased height and prognathism (A) and enlarged hand (B) and foot (C) of the affected twin are apparent. Their clinical features began to diverge at the age of ~13 years. (Reproduced with permission from RF Gagel, IE McCutcheon. Images in clinical medicine. Pituitary gigantism. N Engl J Med 340:524, 1999.) treatment for preoperative shrinkage of large invasive macroadeno mas, immediate relief of debilitating symptoms, and reduction of GH hypersecretion; in frail patients experiencing morbidity; and in patients who decline surgery or when surgery fails to achieve bio chemical control. Irradiation or repeat surgery may be required for patients who cannot tolerate or do not respond to adjunctive medi cal therapy. The high rate of late hypopituitarism and the slow rate (5–15 years) of biochemical response are the main disadvantages of radiotherapy. Irradiation is also relatively ineffective in normal izing IGF-1 levels. Stereotactic ablation of GH-secreting adenomas by Gamma Knife radiotherapy is promising, but long-term results and side effects appear similar to those observed with conventional radiation. SRLs may be required while awaiting the full benefits of radiotherapy. Systemic comorbid sequelae of acromegaly, including cardiovascular disease, diabetes, and arthritis, should be managed aggressively. Mandibular surgical repair may be indicated. SURGERY Transsphenoidal surgical resection by an experienced surgeon is the preferred primary treatment for both microadenomas (remission rate ~70%) and macroadenomas (<50% in remission). Soft tissue swelling improves immediately after tumor resection. GH levels return to normal within an hour, and IGF-1 levels are normalized within 3–4 days. In ~10% of patients, acromegaly may recur several years after apparently successful surgery; hypopituitarism develops in up to 15% of patients after surgery. SOMATOSTATIN RECEPTOR LIGANDS SRLs exert their therapeutic effects through SST2 and SST5 receptor subtypes, both expressed by GH-secreting tumors. The preferred medical treatments for patients with acromegaly include long-acting injectable SRL depot formulations of octreo tide and lanreotide as well as oral octreotide capsules. Although responses vary widely in individual patients, meta-analyses indi cate that GH and IGF-1 levels are normalized in ~50% of patients. Octreotide acetate is an eight-amino-acid synthetic somatosta tin analogue. In contrast to native somatostatin, the analogue is

 relatively resistant to plasma degradation. It has a 2-h serum halflife and possesses 40-fold greater potency than native somatostatin to suppress GH. Octreotide LAR is a sustained-release, long-acting formulation of octreotide incorporated into microspheres that sus tain drug levels for several weeks after intramuscular injection. GH suppression occurs for as long as 6 weeks after a 30-mg intra muscular injection; long-term

monthly treatment sustains GH and IGF-1 suppression and also reduces pituitary tumor size in ~50% of patients. Lanreotide, in a slow-release depot SRL preparation, is a cyclic somatostatin octapeptide analogue that suppresses GH and IGF-1 hypersecretion after a 60-mg subcutaneous injection. Longterm (every 4–6 weeks) administration controls GH hypersecretion in about two-thirds of treated patients and improves patient compli ance because of the long interval required between drug injections. Oral octreotide capsules (40–80 mg daily) maintain biochemical control in patients previously maintained on injectable formula tions. Rapid relief of headache and soft tissue swelling occurs in ~75% of patients within days to weeks of SRL initiation. Most patients report symptomatic improvement, including amelioration of headache, perspiration, obstructive apnea, and cardiac failure. Pasireotide LAR, a multireceptor ligand with preferential SST5 bind ing, has been shown to exhibit efficacy in achieving biochemical control in patients resistant to octreotide or lanreotide preparations. Side Effects SRLs are well tolerated in most patients. Adverse effects are similar for injectable octreotide and lanreotide as well as for oral octreotide formulation. They are short-lived and mostly relate to drug-induced suppression of gastrointestinal motility and secretion. Transient nausea, abdominal discomfort, fat malabsorp tion, diarrhea, and flatulence occur in one-third of patients, and these symptoms usually remit within 2 weeks. Gallbladder contrac tility and emptying are attenuated; up to 30% of patients develop long-term echogenic sludge or asymptomatic cholesterol gallstones. Other side effects include mild glucose intolerance due to transient insulin suppression, asymptomatic bradycardia, hypothyroxinemia, and local injection site discomfort. Pasireotide is associated with similar gastrointestinal side effects but with a higher prevalence of glucose intolerance and new-onset diabetes mellitus.

GH-secreting pituitary tumor Surgery Well controlled Cabergolineb Monitor IGF-1 Well controlled Not controlled Not controlled PART 12 Endocrinology and Metabolism SRL Not controlled Well controlled Increase SRL dose Monitor IGF-1 Pegvisomant Reoperation Well controlled Monitor IGF-1 Radiotherapy Pasireotide + pegvisomant FIGURE 392-8 Management of acromegaly. aIf curative surgery is not feasible. bConsider in cases of mild postoperative GH/IGF-1 elevations. GH, growth hormone; IGF, insulin-like growth factor; SRL, somatostatin receptor ligand (injectable or oral octreotide, or lanreotide). GH RECEPTOR ANTAGONIST Pegvisomant antagonizes endogenous GH action by blocking peripheral GH binding to its receptor. Consequently, serum IGF-1 levels are suppressed, reducing the deleterious effects of excess endogenous GH. Pegvisomant is administered by daily subcu taneous injection (10–30 mg) and normalizes IGF-1 in ~70% of patients. GH levels, however, remain elevated as the drug does not target the pituitary adenoma. Side effects include reversible liver enzyme elevation, lipodystrophy, and injection site pain. Tumor size should be monitored by MRI. Combined treatment with monthly SRLs and weekly or biweekly pegvisomant injections has been used effectively in treatmentresistant patients. DOPAMINE AGONISTS Very high doses of cabergoline (0.5 mg/d) may achieve short-lived and modest GH therapeutic efficacy. Combined treatment with octreotide and cabergoline may induce additive biochemical con trol compared with either drug alone. RADIATION THERAPY External radiation therapy or high-energy stereotactic techniques are used as adjuvant therapy for acromegaly. An advantage of radiation is that patient compliance with long-term treatment is not required. Tumor mass is reduced, and GH levels are attenuated over time. However, 50% of patients require at least 8 years for GH levels to be suppressed to <5 μg/L; this level of GH reduction is achieved in ~90% of patients after 18 years but represents suboptimal GH

Primary SRLa Monitor IGF-1 Not controlled SRL + pegvisomant Pasireotide Well controlled Monitor IGF-1 Not controlled Re-operation suppression. Patients may require interim medical therapy for several years before attaining maximal radiation benefits. Most patients also experience hypothalamic-pituitary damage, leading to gonadotropin, ACTH, and/or TSH deficiency within 10 years of therapy. SUMMARY Surgery is the preferred primary treatment for GH-secreting micro adenomas (Fig. 392-8). The high frequency of residual GH hyperse cretion after macroadenoma resection usually necessitates adjuvant or primary medical therapy for these larger tumors. Patients unable to receive or respond to unimodal medical treatment may benefit from combined treatments, or they can be offered radiation. Very rarely, repeat surgery may be required. ■ ■CUSHING'S DISEASE (ACTH-PRODUCING ADENOMA) (See also Chap. 398) Etiology and Prevalence Pituitary corticotrope adenomas (Cushing's disease) account for 70% of patients with endogenous causes of Cushing's syndrome. However, it should be emphasized that iatrogenic hypercortisolism is the most common cause of cushingoid features. Ectopic tumor ACTH production, cortisol-producing adrenal adenomas, adrenal carcinoma, and adrenal hyperplasia account for the other causes; rarely, ectopic tumor CRH production is encountered. ACTH-producing adenomas account for ~10–15% of all pituitary tumors. Because the clinical features of Cushing's syndrome often lead to early diagnosis, most ACTH-producing pituitary tumors are

TABLE 392-7 Clinical Features of Cushing's Syndrome (All Ages) SYMPTOMS/SIGNS FREQUENCY, % Obesity or weight gain (>115% ideal body weight)

Thin skin

Moon facies

Hypertension

Purple skin striae

Hirsutism

Menstrual disorders (usually amenorrhea)

Plethora

Abnormal glucose tolerance

Impotence

Proximal muscle weakness

Truncal obesity

Acne

Bruising

Mental changes

Osteoporosis

Edema of lower extremities

Hyperpigmentation

Hypokalemic alkalosis

Diabetes mellitus

Source: Adapted with permission from MA Magiokou et al, in Wierman ME: Diseases of the Pituitary. Totowa, NJ: Humana; 1997. relatively small microadenomas. However, macroadenomas also are seen and some ACTH-expressing adenomas are clinically silent. Cush ing's disease is 5–10 times more common in women than in men. These pituitary adenomas exhibit unrestrained ACTH secretion, with resultant hypercortisolemia. However, they retain partial suppress ibility in the presence of high doses of administered glucocorticoids, providing the basis for dynamic testing to distinguish pituitary from nonpituitary causes of Cushing's syndrome. Presentation and Diagnosis The diagnosis of Cushing's syn drome presents two great challenges: (1) to distinguish patients with pathologic cortisol excess from those with physiologic or other dis turbances of cortisol production and (2) to determine the etiology of pathologic cortisol excess. Typical features of chronic cortisol excess include thin skin, central obesity, hypertension, plethoric moon facies, purple striae and easy bruisability, glucose intolerance or diabetes mellitus, gonadal dysfunc tion, osteoporosis, proximal muscle weakness, signs of hyperandrogen ism (acne, hirsutism), and psychological disturbances (depression, mania, and psychoses) (Table 392-7). Hematopoietic features of hypercortisolism include leukocytosis, lymphopenia, and eosinopenia. Immune suppression includes delayed hypersensitivity and infection propensity. These protean yet commonly encountered manifestations of hypercortisolism make it challenging to decide which patients man date formal laboratory evaluation. Certain features make pathologic causes of hypercortisolism more likely; they include characteristic central redistribution of fat, thin skin with striae and bruising, and proximal muscle weakness. In children and young females, early osteo porosis may be particularly prominent. The primary cause of death is cardiovascular disease, but life-threatening infections and risk of suicide are also increased. Rapid development of features of hypercortisolism associated with skin hyperpigmentation and severe myopathy suggests an ectopic tumor source of ACTH. Hypertension, hypokalemic alkalosis, glucose intolerance, and edema are also more pronounced in these patients. Serum potassium levels <3.3 mmol/L are evident in ~70% of patients with ectopic ACTH secretion but are seen in <10% of patients with pituitary-dependent Cushing's syndrome. Laboratory Investigation The diagnosis of Cushing's disease is based on laboratory documentation of endogenous hypercortisolism.

Measurement of 24-h UFC is a precise and cost-effective screening test. Alternatively, the failure to suppress plasma cortisol after an overnight 1-mg dexamethasone suppression test can be used to identify patients with hypercortisolism. As nadir levels of cortisol occur at night, ele vated midnight serum or salivary samples of cortisol are suggestive of Cushing's disease. Basal plasma ACTH levels often distinguish patients with ACTH-independent (adrenal or exogenous glucocorticoid) from

those with ACTH-dependent (pituitary, ectopic ACTH) Cushing's syn drome. Mean basal ACTH levels are about eightfold higher in patients with ectopic ACTH secretion than in those with pituitary ACTHsecreting adenomas. However, extensive overlap of ACTH levels in these two disorders precludes using ACTH measurements to make the distinction. Preferably, dynamic testing based on differential sensitiv ity to glucocorticoid feedback or ACTH stimulation in response to CRH or cortisol reduction is used to distinguish ectopic from pituitary sources of excess ACTH (Table 392-8). Very rarely, circulating CRH levels are elevated, reflecting ectopic tumor-derived secretion of CRH and often ACTH. For further discussion of dynamic testing for Cushing's syndrome, see Chap. 398.

Pituitary Tumor Syndromes CHAPTER 392 Most ACTH-secreting pituitary tumors are <5 mm in diameter, and about half are undetectable by sensitive MRI. The high prevalence of incidental pituitary microadenomas diminishes the ability to distin guish ACTH-secreting pituitary tumors accurately from nonsecreting incidentalomas. Inferior Petrosal Venous Sampling Because pituitary MRI with gadolinium enhancement is insufficiently sensitive to detect small (<2 mm) pituitary ACTH-secreting adenomas, bilateral inferior petrosal sinus ACTH sampling before and after CRH administration may be required to distinguish these lesions from ectopic ACTH-secreting tumors that may have similar clinical and biochemical characteristics. Simultaneous assessment of ACTH in each inferior petrosal vein and TABLE 392-8 Differential Diagnosis of ACTH-Dependent Cushing's Syndromea ACTH-SECRETING PITUITARY TUMOR ECTOPIC ACTH SECRETION Etiology Pituitary corticotrope adenoma Plurihormonal adenoma Bronchial, abdominal carcinoid Small-cell lung cancer Thymoma, other sources Sex F > M M > F Clinical features Slow onset Rapid onset Pigmentation Severe myopathy Serum potassium

<3.3 µg/L <10% 75% 24-h UFC High High Basal ACTH level Inappropriately high Very high Dexamethasone suppression 1 mg overnight Low-dose (0.5 mg q6h) Cortisol >5 µg/dL Cortisol >5 µg/dL High-dose (2 mg q6h) Cortisol <5 µg/dL Cortisol >5 µg/dL UFC >80% suppressed Microadenomas: 90% Macroadenomas: 50% 10% Inferior petrosal sinus sampling Basal central: peripheral

> 2 <2 CRH-induced central: peripheral 3 <3 aACTH-independent causes of Cushing's syndrome are diagnosed by suppressed ACTH levels and an adrenal mass in the setting of hypercortisolism. Iatrogenic Cushing's syndrome is excluded by history. Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; F, female; M, male; UFC, urinary free cortisol.

in the peripheral circulation provides a strategy for confirming and localizing pituitary ACTH production. Sampling is performed at base line and 2, 5, and 10 min after intravenous CRH (1 µg/kg) injection. An increased central:peripheral ACTH ratio (>2) before and a peak central:peripheral ACTH ratio >3 after CRH injection confirm the presence of a pituitary ACTH-secreting adenoma. The sensitivity of this test is >95%, with very rare false-positive results. False-negative results may be encountered in patients with aberrant venous drainage. Petrosal sinus catheterizations are technically difficult, and ~0.05% of patients develop neurovascular complications. The procedure should not be performed in patients with hypertension, in patients

with known cerebrovascular disease, or in the presence of a well-visualized pituitary adenoma on MRI.

PART 12 Endocrinology and Metabolism TREATMENT Cushing’s Disease Selective transsphenoidal resection is the treatment of choice for Cushing’s disease (Fig. 392-9). The remission rate for this proce dure is ~80% for microadenomas but <50% for macroadenomas. However, surgery is rarely successful when the adenoma is not vis ible on MRI. After successful tumor resection, most patients experi ence a postoperative period of symptomatic ACTH deficiency that may last up to 12 months. This usually requires low-dose cortisol replacement, as patients experience steroid withdrawal symptoms and have a suppressed hypothalamic-pituitary-adrenal axis. Bio chemical recurrence occurs in ~5% of patients in whom surgery was initially successful. As persistent hypercortisolemia may cause blood clotting defects, prophylactic postoperative thromboembolic management has been advocated for vulnerable patients. When initial surgery is unsuccessful, repeat surgery is sometimes indicated, particularly when a pituitary source for ACTH is well documented. In older patients, in whom issues of growth and fertil ity are less important, hemi- or total hypophysectomy may be nec essary if a discrete pituitary adenoma is not recognized. Pituitary irradiation may be used after unsuccessful surgery, but it cures only ~15% of patients. Because the effects of radiation are slow and only partially effective in adults, adrenal-targeted steroidogenic inhibi tors are used in combination with pituitary irradiation to block adrenal responses to persistently high ACTH levels. ACTH-dependent hypercortisolism Pituitary MRI Petrosal sinus ACTH sampling* Consider chest/abdomen imaging Ectopic ACTH excluded ACTH-secreting pituitary adenoma Pasireotide and/or Glucocorticoid receptor antagonist Transsphenoidal surgical resection and/or Steroidogenic inhibitors Biochemical cure Persistent hypercortisolism and/or Pituitary irradiation Glucocorticoid replacement, if needed ?Irradiation Follow-up: Adrenalectomy Serial biochemical and MRI evaluation Risk of Nelson’s syndrome FIGURE 392-9 Management of Cushing’s disease. ACTH, adrenocorticotropin hormone; MRI, magnetic resonance imaging; ∗, Not usually required.

Pasireotide LAR 10–40 mg intramuscularly, an SRL with high affinity for SST5 > SST2 receptor subtypes, may control hypercor tisolemia in a subset of patients with ACTH-secreting pituitary tumors when surgery is not an option or has not been successful. The drug lowers plasma ACTH levels and normalizes 24-h UFC levels in ~20% of patients, and up to 40% of patients may experience pituitary tumor shrinkage. Side effects are similar to those encoun tered for other SRLs and include transient abdominal discomfort, diarrhea, nausea, and gallstones (20% of patients). Notably, hyper glycemia and new-onset diabetes develop in up to 70% of patients, likely due to suppressed pancreatic secretion of insulin and incre tins. Because patients with hypercortisolism are insulin-resistant, hyperglycemia should be rigorously managed. The drug requires consistent long-term administration. Osilodrostat (2 mg twice daily titrated up to 30 mg twice daily), an oral 11β-hydroxylase inhibitor that blocks adrenal gland cortisol biosynthesis, normalized 24-h UFC in 86% of patients. Mild, mostly transient gastrointestinal symptoms are common. Patients should be closely monitored for development of hypocortisolism and adre nal insufficiency. Elevated adrenal hormone precursors may lead to hypokalemia and hypertension. QTc prolongation and possibly increased tumor volume are also reported. Ketoconazole, an imidazole derivative antimycotic agent, inhib its several P450 enzymes and effectively lowers cortisol in most patients with Cushing’s disease when administered twice daily (600–1200 mg/d). Elevated hepatic transaminases, gynecomastia, impotence, gastrointestinal upset, and edema are common side effects. Levoketoconazole, a 2S,4R enantiomer of ketoconazole, is admin istered at the same

dose/schedule as ketoconazole and has a similar side effect profile. Mifepristone (300–1200 mg/d), a glucocorticoid receptor antago nist, blocks peripheral cortisol action and is approved to treat hyperglycemia in Cushing's disease. Because the drug does not target the pituitary tumor, both ACTH and cortisol levels remain elevated, thus obviating a reliable circulating biomarker. Side effects are largely due to general antagonism of other steroid hormones and include hypokalemia, endometrial hyperplasia, hypoadrenal ism, and hypertension. Metyrapone (2–4 g/d) inhibits 11β-hydroxylase activity and nor malizes plasma cortisol in up to 75% of patients. Side effects include nausea and vomiting, rash, and exacerbation of acne or hirsutism. Mitotane (3–6 g/d orally in four divided doses) suppresses cortisol hypersecretion by inhibiting 11β-hydroxylase and cholesterol sidechain cleavage enzymes and by destroying adrenocortical cells. Side effects of mitotane include gastrointestinal symptoms, dizziness, gynecomastia, hyperlipidemia, skin rash, and hepatic enzyme eleva tion. It also may lead to hypoaldosteronism. Other agents include aminoglutethimide (250 mg tid), trilostane (200–1000 mg/d), cypro heptadine (24 mg/d), and IV etomidate (0.3 mg/kg per h). Glucocor ticoid insufficiency is a potential side effect of agents used to block steroidogenesis. The use of steroidogenic inhibitors has decreased the need for bilateral adrenalectomy. Surgical removal of both adrenal glands corrects hypercortisolism but may be associated with significant morbidity rates and necessitates permanent glucocorticoid and min eralocorticoid replacement. Adrenalectomy in the setting of residual corticotrope adenoma tissue predisposes to the development of Nelson's syndrome, a disorder characterized by rapid pituitary tumor enlargement and increased pigmentation secondary to high ACTH levels. Prophylactic radiation therapy may be indicated to prevent the development of Nelson's syndrome after adrenalectomy. ■ ■NONFUNCTIONING AND GONADOTROPINPRODUCING PITUITARY ADENOMAS Etiology and Prevalence Nonfunctioning pituitary adenomas include those that secrete little or no pituitary hormones into the systemic circulation, as well as tumors that produce too little hormone

to result in recognizable clinical features. They are the most common type of pituitary adenoma and are usually macroadenomas at the time of diagnosis because clinical features are not apparent until tumor mass effects occur. Based on immunohistochemistry, most clinically non functioning adenomas can be shown to originate from gonadotrope cells or from pituitary null cells. These tumors typically produce small amounts of intact gonadotropins (usually FSH) as well as uncombined α, LH β, and FSH β subunits. Tumor secretion may lead to elevated α and FSH β subunits and, very rarely, to increased LH β subunit lev els. Some adenomas express α subunits without FSH or LH. A TRH stimulation test often induces an atypical increase of tumor-derived gonadotropins or subunits. Presentation and Diagnosis Clinically nonfunctioning tumors often present with optic chiasm pressure and other symptoms of local expansion or may be incidentally discovered on an MRI performed for another indication (incidentaloma). Rarely, menstrual disturbances or ovarian hyperstimulation occur in women with large tumors that pro duce FSH and LH. In these cases, ovaries may have features that resem ble polycystic ovarian syndrome and may produce very high levels of estrogen. More commonly, adenoma compression of the pituitary stalk or surrounding pituitary tissue leads to attenuated LH and features of hypogonadism. PRL levels are usually slightly increased, also because of stalk compression. It is important to distinguish this circumstance from true prolactinomas, as nonfunctioning tumors do not shrink in response to treatment with dopamine agonists. Laboratory Investigation The goal of laboratory testing in clini cally nonfunctioning tumors is to classify the type of tumor, identify hormonal markers of tumor activity, and detect possible hypopituita rism. Free α subunit levels may be elevated in 10–15% of patients with nonfunctioning tumors. In female patients, peri- or postmenopausal basal FSH

concentrations are difficult to distinguish from tumorderived FSH elevation. Premenopausal women have cycling FSH levels, also preventing clear-cut diagnostic distinction from tumor-derived FSH. In men, gonadotropin-secreting tumors may be diagnosed because of slightly increased gonadotropins (FSH > LH) in the setting of a pituitary mass. Testosterone levels are usually low despite the nor mal or increased LH level, perhaps reflecting reduced LH bioactivity or the loss of normal LH pulsatility. Because this pattern of hormone test results is also seen in primary gonadal failure and, to some extent, with aging (Chap. 403), the finding of increased gonadotropins alone is insufficient for the diagnosis of a gonadotropin-secreting tumor. In the majority of patients with gonadotrope adenomas, TRH adminis tration stimulates LH β subunit secretion; this response is not seen in Nonfunctioning Pituitary Mass Differential diagnosis based on MRI and clinical features Dynamic pituitary reserve testing Nonfunctioning adenoma Microadenoma Macroadenoma Low risk of visual loss Observe Surgery Follow-up: MRI MRI Trophic hormone testing and replacement FIGURE 392-10 Management of a nonfunctioning pituitary mass. MRI, magnetic resonance imaging.

normal individuals. GnRH testing, however, is not helpful for making the diagnosis. For nonfunctioning and gonadotropin-secreting tumors, the diagnosis usually rests on immunohistochemical analyses of surgi cally resected tumor tissue, as the mass effects of these tumors usually necessitate resection.

Although acromegaly or Cushing’s disease usually presents with unique clinical features, clinically inapparent (silent) somatotrope or corticotrope adenomas may only be diagnosed by immunostaining of resected tumor tissue. These silent tumors usually grow more aggres sively and account for up to 20% of all nonfunctioning adenomas. If PRL levels are <100 μg/L in a patient harboring a pituitary mass, a nonfunctioning adenoma causing pituitary stalk compression should be considered. Pituitary Tumor Syndromes CHAPTER 392 TREATMENT Nonfunctioning and Gonadotropin-Producing Pituitary Adenomas As the probability of nonfunctioning microadenoma growth is very low, asymptomatic small nonfunctioning microadenomas with no threat to vision may be followed with an MRI after 3 years, with serial MRI and visual field testing thereafter as needed. However, for macroadenomas, transsphenoidal surgery is indicated to reduce tumor size and relieve compressive mass effects (Fig. 392-10). Although it is not usually possible to remove all adenoma tissue surgically, vision improves in 70% of patients with preoperative visual field defects. Preexisting hypopituitarism that results from tumor mass effects may improve or resolve completely. Beginning ~6 months postoperatively, MRI scans should be performed yearly to detect whether tumor regrowth is occurring. Within 5–6 years after successful surgical resection, ~15% of nonfunctioning tumors recur. When substantial tumor remains after transsphenoidal sur gery, adjuvant radiotherapy may be indicated to prevent persistent tumor regrowth. Radiotherapy may be deferred if no postoperative residual mass is evident. Nonfunctioning pituitary tumors respond poorly to dopamine agonist treatment, and SRLs are largely ineffec tive for shrinking these tumors. ■ ■TSH-SECRETING ADENOMAS TSH-producing macroadenomas are very rare but are often large and locally invasive when they occur. Patients usually present with thyroid goiter and hyperthyroidism, reflecting chronic overproduction of TSH. Other sellar mass (not adenoma) Exclude aneurysm Surgery Histologic diagnosis May require disease-specific therapy MRI Trophic hormone testing and replacement

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