Neurosurg Clin N Am 14 (2003) 41–54

NEUROSURGERY CLINICS OF NORTH AMERICA

Pituitary tumor endocrinopathies and their endocrine evaluation

Marie F. Simard, MD

Department of Neurosurgery, University of Utah Medical Center, Suite 3B409, 30 North 1900 East, Salt Lake City, UT 84132–2303, USA

Prolactinomas

Background

Prolactin (PRL)-secreting pituitary adenomas comprise approximately 30% to 50% of endocrinologically active neoplasms of the hypophysis in adults as well as in children [1–3]. Men usually present with signs and symptoms related to mass effect and with larger tumors compared to women. Prolactinomas occurring in 20% of patients with the multiple endocrine neoplasia-1 (MEN-1) syndrome (neuroendocrine lesions of the gastrointestinal tract, primary hyperparathyroidism, and pituitary adenomas) tend to be more aggressive than the sporadic type [4]. Hyperprolactinemia may be a functional abnormality in a large subgroup of women with or without a demonstrable microadenoma and appears to be self-limiting in up to one third of women [5]. Pregnancy may trigger a return to normal function [5]. Ten percent of patients with idiopathic hyperprolactinemia develop microadenomas [6]. The risk of progression from a microadenoma to a macroadenoma is 7% over a period of 6 years [7].

The differential diagnosis of hyperprolactinemia is extensive and includes (1) the use of medications, such as neuroleptics, tricyclic antidepressants, monoamine oxidase inhibitors, serotonin reuptake inhibitors, alpha-methyldopa, reserpine, verapamil, protease inhibitors, opiates, and cocaine; (2) conditions such as renal insufficiency, cirrhosis, primary hypothyroidism, adrenal insufficiency, and chest wall and cervical cord lesions; (3) suckling, lesions of the hypothalamus and masses compressing the pituitary stalk, which elevates PRL to levels usually less than 150 ng/mL; and (4) extremely rarely, the ectopic production of PRL [6].

Endocrinopathy

Elevated PRL levels suppress the hypothalamic-pituitary-gonadal axis. Approximately one third of female patients manifest amenorrhea or menstrual abnormalities and infertility. Men present with decreased libido, impotence, oligospermia, and infertility. Hypogonadism may also lead to dyspaneurea and osteoporosis [8]. Galactorrhea is present in 80% of women and approximately 30% of men [8]. Increased body weight may be associated with hyperprolactinemia [9]. Children may present with delayed puberty and arrest of growth [1].

Diagnostic evaluation

The initial endocrine evaluation should include measurements of basal morning serum PRL, free thyroid hormones, thyrotropin (TSH), and serum insulin-like growth factor-1 (IGF-1) to rule out growth hormone (GH) cosecretion by the adenoma. Screening blood chemistry and pregnancy testing should be performed. The finding of minimally elevated serum PRL levels requires confirmation in several samples taken in the morning [8]. PRL-secreting macroadenomas are associated with PRL levels greater than 250 ng/mL, and the size of the tumor correlates with the PRL level [6]. When hypogonadism is suspected, serum testosterone or estradiol should be measured in men and women, respectively.

E-mail address: william.couldwell@hsc.utah.edu.

PII: S1042-3680(02)00036-0

Prolactinomas secreting large amounts of PRL may give false low plasma values in the range of 30 to 200 μg/L when measured by the two-site monoclonal immunoradiometric assay (IRMA) or by the chemiluminometric assay (ICMA) [10]. The inaccurate measurement of PRL excess has been called the "high dose hook effect" and affects the measurement of serum PRL in approximately 6% to 14% of patients with large pituitary tumors, usually young men [10–12]. Serum PRL concentrations should be measured in an undiluted serum sample as well as after a 1:100 dilution [10].

Reported sensitivities of MRI in the detection of microprolactinomas are approximately 55% to 90% for contrast-enhanced studies [13]. At a PRL level of 52 ng/mL, the estimated probability of a microadenoma is approximately 51% [13]. An incidental nonsecreting pituitary tumor may be present in a patient with hyperprolactinemia [14]. Because of its cost, in vivo imaging of tumor dopamine receptors by means of radiolabeled dopamine D_2 receptor radioligands is of limited value [8]. Visual fields (Goldmann perimetry) are indicated in patients with tumors adjacent to or pressing on the optic chiasm as visualized on MRI [6]. During pregnancy, tumor expansion of macroprolactinomas should be monitored by means of PRL levels and visual field perimetry [8].

Gonadotroph cell adenomas

Background

Approximately one third of all pituitary adenomas are nonsecretory [15]. Many of these lesions actually secrete, although inefficiently [16], gonadotropins or their subunits [15,17]. Gonadotropin-secreting adenomas constitute 40% to 50% of all macroadenomas [16] and 7% to 15% of all pituitary adenomas in adults [3]. These tumors are extremely rare in children [1]. They affect both genders equally with a wide age range [3], although most patients are diagnosed late in life. Thus, despite hypersecretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), no distinct hormone-dependent clinical syndrome is present in most cases [15]. Patients usually seek medical attention for neurologic symptoms resulting from mass effect or symptoms of invasion by the gonadotroph adenomas, which can measure up to several centimeters in diameter [15,17]. Bitemporal hemianopsia is the most common type of visual deficit [16]. The patient may also present with symptoms related to increased intracranial pressure and hypothalamic compression [17].

Endocrinopathy

Complete or partial anterior pituitary failure is present in approximately 75% of patients [15]. Central hypogonadism is noted in approximately 60% of men, who may present with symmetric testicular atrophy (mean testicular length of less than 3 cm), loss of libido, or impotence. Premenopausal female patients may present with oligomenorrhea or amenorrhea and infertility [15,17]. Central hypothyroidism and hypocortisolism are detected in 34% and 26% of patients, respectively [15]. Hypopituitarism, when secondary to intrasellar pressure increase, may be reversible with therapy [15]. Severe hyperstimulation of the ovaries has been documented in a 34-year-old woman with a huge pituitary gonadotroph adenoma [18]. Rarely, hypersecretion of LH may cause precocious puberty in boys [19,20].

Diagnostic evaluation

Evaluating the patient for hypopituitarism consists of measuring plasma LH, FSH, testosterone, estradiol, PRL, TSH, free thyroid hormones, corticotropin, cortisol, and IGF-1. Central hypogonadism with inappropriately low gonadotropin levels and a serum total testosterone concentration below 300 ng/dL are noted in more than one half of male patients [15]. Hyperprolactinemia has been reported in 33% of patients, irrespective of gender, with a maximal value of 110 ng/mL [15].

Careful measurements of basal and thyrotropin-releasing hormone (TRH)–stimulated gonadotropins and subunits should be conducted [17]. Immunometric and immunofluorimetric assays for intact LH measurement avoid cross-reactivity with the α-subunit molecule and are preferable [16]. In approximately 50% to 75% of patients, secretion of the combination of intact FSH (>10 IU/L in men) and α-subunit, FSH-β subunit, and LH-β subunit can be documented in vivo [16,21]. Gonadotropinomas may also secrete α-subunit and β-subunit of LH and FSH alone [15,17]. Intact LH excess secretion is much rarer (>10 IU/L) and elevates serum testosterone levels in male patients [17]. In normal men and women, the administration of TRH causes an absent FSH response [17] and an increase in intact LH and LH β-subunit of no more than 33% [16]. Similarly, in primary hypogonadism, LH and FSH are elevated, and neither intact gonadotropins nor their subunits

respond to TRH [16]. Measurement of the LH β-subunit, intact LH and FSH, and α-subunit responses to TRH (500 μg intravenously) has been shown to identify approximately 50% and 69% of gonadotropin tumors in men and women, respectively [22,23]. TRH-stimulated LH β-unit secretion seems to be the most sensitive test, resulting in elevated levels in 36% of men [23] and 68% of women [22] harboring clinically nonfunctioning pituitary tumors. Patients with gonadotropin-producing pituitary tumors may have a greater than 60% increment in plasma LH β-subunit level in response to the administration of TRH [22,23]. Because gonadotropin levels are elevated in postmenopausal women, the in vivo diagnosis of a gonadotroph cell adenoma rests on finding a response to TRH of intact FSH or LH or, most commonly, of LH β-subunit [16].

T1-weighted coronal spin-echo MRI images before and after gadolinium administration detect approximately 90% of nonfunctioning adenomas [24]. In vivo labeling of pituitary dopamine D_2 receptor by scintigraphy has been shown to correlate with the tumor size response to quinagolide, a dopamine agonist [25,26]. The radiolabeled somatostatin analogue ^{111}indium-pentetreotide, employed as an in vivo imaging modality, has shown heterogeneous labeling of nonfunctioning tumors, and the results have failed to correlate with the therapeutic response to octreotide [27,28]. Visual acuity assessment and neuro-ophthalmic evaluation of the visual fields, including computerized tests, should be performed in patients harboring macroadenomas [16].

Acromegaly

Background

The average incidence of GH-secreting pituitary adenomas is estimated at 3.3 cases per million per year [29], with men and women being equally affected [30–35]. Patients usually present in their fourth decade, after the insidious onset and slow progression of the disease over several years [3,36]. Somatotropinomas constitute approximately 20% of all pituitary tumors and present as macroadenomas in approximately 75% of patients [3]. In children less than 20 years of age, GH-secreting pituitary adenomas represent 8% of pituitary tumors [1], the mean age at the onset of symptoms is 10.7 years (range: 4–16 years) [30], and the mean preoperative duration of symptoms is 3.1 years (range: 0.5–6 years) [30]. GH-secreting tumors in pediatric patients are more likely to be locally invasive (40% of cases) or aggressive [30].

Plurihormonal GH adenomas cosecrete PRL, TSH, corticotropin, or α-subunit [3,36]. Somatotropinomas are associated with the McCune-Albright syndrome (polyostotic fibrous dysplasia, cafe-au-lait pigmentation, and precocious puberty), MEN-1 syndrome, and Carney syndrome (skin and cardiac myxomas, Cushing's syndrome, and somatotropinomas) [36,37]. Excess growth hormone releasing hormone (GHRH) causes pituitary somatotroph hyperplasia and usually originates from carcinoid tumors or, rarely, from central hypothalamic hamartomas, gliomas, and gangliocytomas [36]. Ectopic GH secretion is rare. Early recognition of GH excess and treatment is important, because acromegaly is associated with reduced life expectancy as a result of vascular, respiratory, and malignant diseases [31,38]. The overall length of survival is decreased by an average of 10 years compared with matched control populations [29]. Normal life expectancy may be restored after reducing GH levels to less than 2.5 μg/L with treatment [29,36,38].

Endocrinopathy

In children, the mean height at the time of surgery is approximately 183 cm. In prepubescent children, the clinical biologic characteristics of acromegaly include rapid linear growth and gigantism as well as precocious puberty. In pubescent children, symptoms include rapid growth, amenorrhea, and hypogonadism. Headaches and visual disturbances are common [1,30]. Approximately half of the affected children have associated hyperprolactinemia or pituitary insufficiency [30].

In adults, the clinical manifestations of acromegaly secondary to high circulating GH and IGF-1 levels include skeletal and soft tissue overgrowth and deformities as well as cardiac, respiratory, neuromuscular, endocrine, and metabolic complications [32,34–36,39–45,47–51] and a propensity toward neoplastic transformation [29,31,33,38, 52,53].

Musculoskeletal system

Periosteal new bone formation causes acral enlargement, mandibular overgrowth, widening of the maxilla, frontal bossing, nasal bone hypertrophy, and enlargement of paranasal sinuses [36,46]. Axial and peripheral monoarticular and polyarticular arthropathy is generally noninflammatory and occurs in approximately 70% of patients [40]. Crepitus, stiffness, hypermobility,

and debilitating joint pain precede the development of chronic osteoarthritis. Joint effusions are rare [36]. Both bone formation and resorption are increased [48]. These patients have osteopenia at trabecular sites on bone mineral density (BMD) studies despite slightly elevated cortical BMD [45]. Gonadal failure may contribute to the osteoporosis [36].

Skin

Oily skin, hyperhidrosis, coarsening of body hair, and Raynaud's phenomenon are common. Thickening of the skin produces facial coarsening, spade-shaped hands, skin tags, and heel pads [36,46].

Cardiovascular system

Atherosclerosis, cardiovascular, and cerebrovascular diseases double the death rate of acromegalic patients compared with the healthy population [54], with approximately 60% of deaths being attributed to cardiovascular disease [32]. Mononuclear cell infiltrates and interstitial fibrosis of the myocardium have been found in up to 80% of acromegalics [55] and involve both ventricles [50]. In the early stages of the disease, some patients present with a hyperkinetic syndrome characterized by an increase in heart rate and cardiac output and a decrease in vascular resistance. Subclinical cardiomyopathy characterized by biventricular diastolic dysfunction at rest and impaired cardiac performance during exercise has been documented in young, normotensive, non-glucose-intolerant acromegalics [32,34,35]. Approximately 20% of patients have symptomatic cardiac disease at the time of diagnosis [32]. Patients also develop systemic hypertension, premature coronary disease, and arrhythmias, particularly ventricular premature beats and intraventricular conduction defects [36,50]. Left untreated, congestive heart failure ensues as a result of left ventricular dilatation and mitral or aortic valve disease [42,50]. The reduction of serum GH and IGF-1 levels improves cardiac function [32].

Respiratory system

Respiratory dysfunction is common in acromegalics. Apnea during sleep is attributed to obstructive tissue thickening along the upper respiratory tract [51] more often than to a central cause [43]. The pharynx of acromegalic patients with sleep-disordered breathing is highly collapsible at both the tongue base and soft palate edges [44]. Thickening of the laryngeal mucosa and vocal cords can produce a deep resonant voice and unilateral or bilateral vocal cord fixation with laryngeal stenosis [51]. Tracheostomy may be required, particularly during anesthesia [36].

Neurologic system

Sensorimotor polyneuropathy in a stocking and glove distribution develops in approximately 50% of patients with acromegaly. Peripheral paresthesias, proximal muscle weakness, myalgias, cramps, carpal tunnel syndrome, and serum creatinine phosphokinase (CPK) elevation also afflict the patient [36,47].

Endocrine system

Hypopituitarism caused by compression of normal pituitary tissue is common. More than 50% of patients have either amenorrhea or impotence, and approximately 25% have secondary thyroid or adrenal failure [36]. Plurihormonal tumors may be associated with hyperthyroidism or, more commonly, hyperprolactinemia in up to 30% of patients [56]. A high prevalence of thyroid enlargement or nodular goiter and an increased risk of colloid, hyperplastic, or adenomatous nodules have been observed [39]. Nodular or diffuse goiter increases the risk of hyperthyroidism [57]. Unfortunately, effective treatment of the acromegaly has little effect on the shrinkage of thyroid nodules [39]. Benign prostatic hyperplasia has been found in 58% of acromegalics compared with 27% of age-matched controls [41]. The prevalence of structural abnormalities of the prostate, including calcifications, nodules, cysts, and vesicle inflammation, (78% versus 23% in controls). Prostatic volume may increase despite the presence of hypogonadism [41].

Metabolism

Chronic GH excess causes insulin resistance in approximately 20% to 30% of patients, who present with impaired glucose tolerance or overt diabetes mellitus (DM) [48]. GH increases amino acid retention and stimulation of protein synthesis, leading to an increase in lean body mass [49]. The antinatriuretic action of GH, when in excess, augments total body water and extracellular fluid volume and may cause mild arterial hypertension [48]. Total body potassium may be increased. GH excess stimulates calcium absorption from the gastrointestinal tract as well as excretion of calcium and phosphate in the urine [48].

Neoplasia

Acromegaly is associated with an increased prevalence of colorectal tubulovillous adenomas and carcinomas [33], which may be secondary to an increase in epithelial cell proliferation [58]. Recent reviews report a 2.5% to 5% incidence of colorectal cancer and a 25% to 45% incidence of colonic adenomas [33,36]. Acromegalics in whom serum IGF-1 remains elevated or who have had a previous adenoma are at high risk of developing subsequent colorectal neoplasia [53]. In patients older than 50 years of age who have had acromegaly for more than 10 years, the presence of three or more skin tags is a reliable screen for colon polyps [59]. An increased prevalence of thyroid carcinoma has been reported in a large series of patients [52].

Psychologic features

Acromegalic individuals suffer from depression, lability of mood, impaired concentration, anxiety and irritability, body image distortions, and social withdrawal [60].

Pregnancy

There have been more than 70 reported cases of pregnancy in acromegalic women in the literature [42,61]. Normalization of GH and PRL levels is often necessary to promote fertility and conception [61]. Pregnancy exacerbated acromegaly in 4 of 24 patients in one series; however, none of the potential complications of acromegaly, such as hypertension, coronary artery disease, or DM, have been shown to have a deleterious effect in acromegalic women during pregnancy [61].

Diagnostic evaluation

Autonomous GH secretion can be reliably confirmed by the oral glucose tolerance test (OGTT). The normal level of postglucose suppression of GH is less than 2 μg/L by radioimmunoassay or less than 1 μg/L by ultrasensitive IRMA or ICMA 1 to 2 hours after an oral glucose load (75 g) [46,62,63]. Biochemical confirmation of the GH hypersecretion requires a random GH level greater than 0.4 μg/L or a GH nadir during the OGTT greater than 2 μg/L or 1 μg/L, depending on the assay utilized, each with elevated sex- and age-matched IGF-1 levels [64,65]. Recent studies have suggested that certain patients with clinical features of acromegaly and elevated IGF-1 levels have GH nadirs less than 1 μg/L during the OGTT [66]. GH levels are normally elevated during adolescence and pregnancy and are decreased by intercurrent illness and malnutrition [46]. Elevated GH levels are generally proportional to tumor size [46].

Distinction between pituitary and extrapituitary disease can be accomplished with MRI. If evidence of a pituitary adenoma is lacking, peripheral GHRH-secreting tumors can be diagnosed by measuring plasma GHRH levels [36]. Chest and abdominal imaging is recommended to localize the source of ectopic GH or GHRH. An empty sella in an acromegalic patient who has no evidence of extrapituitary tumor is suggestive of prior pituitary infarction [36].

Scintigraphy using octreotide complexed to ^{111}In by diethylene triamine pentaacetic acid (DTPA) provides an imaging technique that allows one to visualize pituitary tumors based on the functional properties of their membrane somatostatin receptors. A significant correlation exists between ^{111}In DTPA accumulation by the adenoma and the effect on plasma GH levels of octreotide administration [27].

Ancillary tests

Screening fasting blood chemistry, urine analysis, and blood cell count are indicated. A careful cardiac evaluation is mandatory in all patients regardless of their age [34]. Investigation of diastolic and systolic function by equilibrium radionuclide angiography is advised at diagnosis and can be useful to monitor abnormalities in cardiac performance during treatment [32]. Acromegalic patients older than 55 years of age with either an elevated serum IGF-1 or a previous adenoma of the bowel need long-term surveillance colonoscopy for colorectal neoplasia, repeated at 3-year intervals [53]. For patients who are either cured of their disease or who have a normal colonoscopic screening after the age of 40 years, 5-year screening intervals might be appropriate [53]. Barium radiography is not reliable because of the hypertrophied colonic mucosa and lengthening of the bowel [36]. BMD and careful prostate screening are recommended. Neuropsychologic assessment may be of benefit to the patient's emotional well being [60]. Overnight sleep studies are required for the evaluation of sleep apnea.

Corticotroph cell adenoma

Background

Cushing's syndrome has a prevalence estimated at approximately 10 per 1 million population [67]. The corticotropin-dependent forms include (1) pituitary corticotroph adenomas or Cushing's

disease (CD) [3]; (2) syndrome of ectopic corticotropin secretion by tumors originating in the lung, bronchus, thymus, or pancreas, by pheochromocytoma and medullary thyroid carcinoma; and (3) the rare ectopic corticotropin-releasing hormone (CRH) secretion usually originating from pheochromocytomas, gangliocytomas, and paragangliomas [68,69].

CD accounts for 70% to 80% of corticotropin-dependent forms of hypercortisolism [67]. Approximately 15% of all pituitary adenomas in adults [3] are corticotropin-secreting tumors, which are fourfold to sixfold more prevalent in women [70] and most often occur between the ages of 20 and 60 years [3]. In children older than 8 years of age, pituitary disease accounts for more than 50% of Cushing's syndrome cases. Corticotropin-secreting pituitary tumors represent approximately 55% of pituitary adenomas diagnosed in children 11 years old or younger and approximately 33% of those diagnosed in children and young adults younger than 20 years of age [1].The disease is equally common in male and female prepubertal children [71].

CD is most often caused by a solitary intrasellar microadenoma. Macroadenomas account for up to 10% of corticotropinomas, with invasiveness being more frequent at a younger age [70]. Cerebrospinal or extracranial metastasis occurs rarely [72]. Nodular corticotroph hyperplasia without evidence of a CRH-secreting neoplasm has been reported in 2% or less of surgical cases [73].

Endocrinopathy

Clinical features highly suggestive of Cushing's syndrome include plethora, increased supraclavicular fullness, central obesity, proximal muscle weakness, cutaneous wasting (skinfold thickness on the dorsum of the hand <2 mm), purple striae more than 1 cm in diameter, spontaneous ecchymosis, osteopenia, hypertension, and growth retardation with delayed bone age in children [70,71]. Other symptoms and signs of hypercortisolemia include papular acne, vellus hypertrichosis of the forehead and upper cheeks, cutaneous and systemic fungal infections, poor wound healing, lipid abnormalities, decreased libido, oligomenorrhea and amenorrhea, infertility, impotence, nephrolithiasis, polyuria, headaches, neuropsychiatric problems ranging from major affective disorders to global psychologic dysfunction, and, rarely, spinal epidural lipomatosis [67,70,74]. A subset of older patients with nonsuppressible long-standing corticotropin-secreting adenomas may present with macronodular adrenal disease and, rarely, with single bilateral adenomas [70]. Nelson's syndrome is characterized by high corticotropin levels and hyperpigmentation. The features typical of Cushing's syndrome may be absent in patients with ectopic corticotropin or CRH secretion [70]. Ectopic corticotropin secretion may, however, typically present in a young male patient with hypokalemia and rapid onset of symptoms [74]. Cyclic or periodic Cushing's syndrome, in which the exacerbation of mild Cushingoid features may parallel fluctuating hormonogenesis, is caused by CD in 50% of cases [75].

Diagnostic evaluation

Screening blood cell count and fasting blood chemistry are indicated, because patients with Cushing's syndrome often present with a white blood cell count of at least 11,000 cells per cubic millimeter [70] and may develop hypokalemic metabolic alkalosis, glucose intolerance, DM, or hyperlipidemia.

The 24-hour urinary free cortisol measurement

Excessive glucocorticoid levels in urine or blood are diagnostic of Cushing's syndrome. Determination of 24-hour urinary free cortisol (UFC) by high-pressure liquid chromatography (HPLC) or immunoassay is the best screening test for Cushing's syndrome [70]. The diagnostic sensitivity and specificity of measurements by HPLC range from 95% to 100% in various series [76]. The diagnosis is unequivocal in a patient with classic features and fourfold normal cortisol excretion (around 400 μg/d in most radioimmunoassays) [70]. In children, UFC should be corrected for body surface area [70]. Pregnancy should allow for a higher upper limit of normal free cortisol measurement. Increased fluid intake augments UFC excretion, and renal insufficiency or low urine volume lowers the amount of cortisol excreted [70]. Results may be falsely positive in patients with pseudo-Cushing's syndrome as a result of endogenous depression, chronic alcoholism, eating disorders, or serious illness [77]. Periodic endogenous hypercortisolism may vary in cycle length from 12 hours to 85 days. If cyclic Cushing's syndrome is suspected based on clinical findings and the initial biochemical evaluation is negative, a repeat evaluation in 3 to 6 months is recommended [78].

Midnight plasma cortisol

Cortisol secretion normally follows a circadian rhythm, peaking in the early morning and at its nadir in the late evening to a few hours after midnight [79]. Patients with Cushing's syndrome fail to decrease cortisol secretion during the normal nadir. Using 5.2 μg/dL (140 nmol/L) as a cutoff, an elevated midnight plasma cortisol level has a sensitivity of 100% and a specificity of 77% for the diagnosis of Cushing's syndrome [79].

The 1-mg overnight dexamethasone suppression test

This test consists of administering 1 mg of dexamethasone at 11:00 pm, with measurement of serum cortisol at 8:00 am the next morning. A normal cortisol level is less than 5 μg/dL (<138 nmol/L). Serum cortisol concentrations greater than 10 μg/mL (>275 nmol/L) are strongly suggestive of Cushing's syndrome. Values between 5 and 10 μg/dL are equivocal. This test has modest diagnostic accuracy because of false-positive results and a sensitivity as low as 55% in cases of mild hypercortisolism [80].

Plasma corticotropin

Once the diagnosis of Cushing's syndrome has been confirmed, the source of hormone excess must be identified. The advent of a sensitive and specific two-site immunometric assay for plasma corticotropin has facilitated the diagnosis of CD [81]. Corticotropin has a short plasma half-life, necessitating that samples be kept in an iced-water bath, centrifuged, aliquoted, and frozen within a few hours to avoid spuriously low results [70]. Simultaneous plasma cortisol levels should be determined [80]. Measured by immunometric assay, plasma corticotropin levels greater than 10 pg/mL (2.2 pmol/L) are suggestive of, and levels greater than 20 pg/mL (4.5 pmol/L) are indicative of a corticotropin-secreting neoplasm [70]. Subnormal corticotropin levels less than 5 pg/mL (1.1 pmol/L) are usually present in patients with corticotropin-independent Cushing's syndrome [74]. Patients with the ectopic corticotropin syndrome generally have high plasma corticotropin values, although these may overlap with those seen in patients with CD [74].

High-dose dexamethasone suppression test

When plasma corticotropin levels are greater than 10 pg/mL, the source of corticotropin secretion (pituitary versus ectopic) must be localized. Corticotropin secretion by corticotropinomas is usually inhibited by high-dose glucocorticoids. The high-dose dexamethasone suppression test (HDDST) is performed by collecting a 24-hour baseline urine sample, administering 2 mg of dexamethasone orally every 6 hours for 2 days, and repeating a 24-hour urine collection during the last 24 hours of the test. In children the dexamethasone dose is weight adjusted [82]. A criterion of 69% suppression from baseline 24-hour UFC is required to yield a specificity of 100% in the diagnostic of CD [67,70].

The 8-mg overnight dexamethasone suppression test

This test is widely used because of its convenience and consists of measuring a baseline plasma cortisol followed by the administration of 8 mg of dexamethasone orally at 11:00 PM. A second plasma cortisol level is drawn 9 hours later at 8:00 AM. As the criterion for CD, a decrease in plasma cortisol of 50% or more yields a diagnostic accuracy comparable to that of the HDDST [67,70]. However, conditions that alter dexamethasone absorption or metabolism confound the results of the HDDST and the overnight dexamethasone suppression test.

Corticotropin-releasing hormone stimulation test

CRH (1 μg/kg or 100 μg intravenously) is administered in the morning and elicits an increase in plasma corticotropin or cortisol in patients with CD, whereas patients with ectopic corticotropin secretion do not respond [83]. A rise in plasma corticotropin values of greater than 35% at 15 and 30 minutes compared with baseline yields a 100% specificity and a 93% sensitivity, and an increase in cortisol of at least 20% in the mean post-CRH value at 30 and 45 minutes yields a specificity of 88% and a sensitivity of 91% in the diagnosis of CD [83].

MRI

MRI of the sella identifies a tumor in approximately two thirds of patients with CD with a specificity of approximately 95% [84]. A precontrast scan must always be performed, because 5% of microadenomas are "soft" and readily visible, becoming isointense with the enhancing pituitary gland on the immediate postgadolinium scan [84].

Bilateral simultaneous inferior petrosal sinus sampling

Inferior petrosal sinus sampling (IPSS) for corticotropin has emerged as the most accurate and reliable means of distinguishing pituitary from nonpituitary corticotropin-dependent Cushing's

syndrome [85–90]. IPSS should be reserved for patients with classic clinical and biochemical CD in whom MRI findings are negative or equivocal, for patients with equivocal suppression and stimulation tests [78], and for patients with a clinical presentation consistent with ectopic corticotropin secretion (male, hypokalemia, or rapid onset of symptoms) [74]. In experienced hands, the diagnostic accuracy of IPSS approaches 80% to 100% [88]. Blood samples are obtained in the basal state and at 3, 5, and 10 minutes after the administration of ovine CRH (1 μg/kg or 100 μg intravenously) from each inferior petrosal sinus (IPS) and a peripheral vein, creating an IPS-to–peripheral corticotropin ratio (IPS/P ratio) [74]. The procedure must be performed when peripheral cortisol levels are elevated to suppress the normal corticotroph population of the anterior pituitary. Determination of midnight plasma cortisol or UFC excretion should thus be performed immediately before IPSS [70]. Peripheral CRH should be measured routinely to exclude the possibility of a nonpituitary neoplasm secreting CRH as the source of hypercortisolism [74]. Corticotropin concentrations are greater in the central samples in CD and increase after CRH administration, reflecting corticotropin secretion by the adenoma. CRH significantly reduces the number of false-negative basal results [89]. In contrast, when corticotropin secretion is ectopic, corticotropin values in the central and peripheral specimens are similar and do not increase after CRH [70]. An IPS/P ratio greater than 3.0 after the administration of CRH is considered consistent with CD. Most patients with ectopic corticotropin syndrome have an IPS/P ratio less than 2.0, and, rarely, certain patients have ratios between 2.0 and 3.0. Bilateral simultaneous sampling is essential, because the maximal basal nondominant IPS/P is less than 2.0 in more than 50% of patients with CD and remains less than 2.0 after ovine CRH administration in 33% of cases [86]. Lateralization of the pituitary microadenoma is defined by a corticotropin IPS gradient. A gradient greater than 1.4 between the IPSs before and after CRH stimulation has a positive predictive value of 74% and 83%, respectively [87,89]. If a reversal of the lateralization gradient is seen from the pre- to post-CRH values, the test cannot be relied on for lateralization [90]. Midline adenomas may cause misleading lateralization gradients [89]. The rate of correlation of the corticotropin IPS gradient with operative outcome ranges from 47% to 75% [85,89]. When a discrepancy exists between imaging and IPSS, IPSS is more likely to agree with the final pathologic finding [89]. IPS sampling has been associated with morbid and even fatal complications, including transient discomfort in the ear during catheterization, deep vein thrombosis, pulmonary emboli, and brain stem vascular damage [85,89,91]. The use of intravenous heparin during the procedure is advocated to help prevent thrombosis [89].

Sampling of the cavernous sinus has yielded a 20% false-negative rate [92] and has a higher incidence of occlusive events [70]. Jugular venous sampling is easier to perform and has a sensitivity of 88% and a specificity of 100% using the same interpretation criteria as for IPSS. This approach may be used as an initial procedure with a referral for IPSS when results are negative [93].

Thyrotroph cell adenomas

Background

TSH-secreting pituitary adenomas are a rare type of glycoprotein hormone–secreting tumor associated with inappropriate TSH secretion and hyperthyroidism. The detection rate of these tumors has increased considerably with the advent of ultrasensitive TSH assays. TSH-secreting tumors occur at a rate of 1 in 1 million in the general population and represent 1% to 2.8% of all pituitary adenomas [3,94–97]. Patients of all ages, with an equal gender predilection, harbor such tumors [94]. However, thyrotropinomas are rare in childhood. Most adenomas secrete TSH alone, often accompanied by hypersecretion of the α-subunit. Mixed hormonal secretion occurs in approximately 30% of patients, with GH being detected in 16%, PRL in 11%, and gonadotropins in 1.4% of cases [94]. Approximately 90% of patients present with macroadenomas of 23 mm in average maximal diameter [94,96]. Extrasellar extension has been documented in approximately two thirds of patients, and invasion of the cavernous and sphenoid sinuses has been reported in 35% [94, 96]. TSH-secreting adenomas have been associated with MEN-I [98] and the McCune-Albright syndrome [99].

Endocrinopathy

In accordance with recent large studies, most patients have symptoms of hyperthyroidism for many years (mean duration of 9 years) preceding the time of diagnosis. Symptoms are most often severe, but can be mild or, less commonly, absent [96]. Manifestations of hyperthyroidism include

goiter, warm moist skin, palmar erythema, friable nails, weight loss despite normal or increased caloric intake, dyspnea on exertion or at rest, resting tachycardia, palpitations, arrhythmias, heart failure, oligomenorrhea or amenorrhea in women, gynecomastia, reduced sperm count and impotence in men, insomnia, irritability, fatigability, typical stare, fine distal tremor, brisk deep tendon reflexes, proximal muscle weakness, osteoporosis, hypercalcemia, mild leukopenia with relative lymphocytosis, and abnormal liver function [100]. Goiter is present in 80% to 94% of patients, including those with previous partial thyroidectomy, and may be multinodular. Thyroid nodules are detected in two thirds of patients, probably as a result of sustained TSH stimulation over many years [96]. One case of thyroid follicular carcinoma has been reported [101]. Features of hyperthyroidism rarely associated with thyrotropinomas include thyrotoxic periodic paralysis (TPP) [102] and Graves bilateral exophthalmos [103]. Unilateral exophthalmos as a result of orbital invasion by the tumor has been reported [94]. Associated hyperprolactinemia may result in menstrual disorders or galactorrhea in up to one third of female patients, decreased libido in men, and delayed puberty in children [94]. Typical features of acromegaly are present when TSH and GH are cosecreted by the tumor. Visual field defects occur in approximately 40% to 50% of cases, and headaches occur in approximately 20% to 40% of patients [94,96].

Diagnostic evaluation

A screening blood chemistry panel and blood cell count are indicated. Baseline endocrine evaluation includes the measurements of serum TSH, free T4, free T3, α-subunit, PRL, and GH concentrations. TSH levels should be measured by a third-generation assay (lower limit of sensitivity of 0.01 mU/L) [104]. Free T4 and free T3 measurements must be performed by a two-step direct method rather than by analogue-based techniques so as to prevent spuriously elevated values caused by variation of thyroid hormone transport proteins [103]. Patients present with detectable TSH levels, which may be normal or low in up to one third of cases, and high free thyroid hormone levels [94]. The lack of correlation between free thyroid hormone and TSH levels has been attributed to enhanced biologic activity of the TSH molecule [105]. In patients previously treated with thyroid ablation, the TSH levels are up to six times higher compared with untreated patients [94], the symptoms of hyperthyroidism are more severe, the tumors tend to be larger, and the visual field impairments are greater. After thyroid ablation, the absence of negative thyroid hormone feedback seems to promote pituitary tumor growth and secretion [96].

α-Subunit hypersecretion is detected in 66% of patients and the α-subunit/TSH molar ratio is elevated in 80% of patients with thyrotropinomas [94]. The ratio is calculated as α-subunit (micrograms per liter)/TSH (milliunits per liter) × 10 and should be interpreted based on the glycoprotein secretory status of the patient [106]. Beck Peccoz et al [106] have established normality guidelines for this ratio: if TSH is normal, the ratio is less than 5.7 in normogonadotropic patients and less than 29.1 in hypergonadotropic patients; if TSH is elevated, the ratio is less than 0.7 in normogonadotropic patients and less than 1.0 in hypergonadotropic patients.

Complimentary tests related to the diagnosis of hyperthyroidism include the measurement of sex hormone–binding globulin (SHBG) (concomitant hypersecretion of GH, however, may inhibit SHBG secretion [94]) and the ^{131}iodine scan of the thyroid gland, which shows a diffuse and increased uptake after 24 hours. Ultrasonography of the thyroid is indicated in patients presenting with a multinodular goiter or suspicious thyroid nodule. The basal metabolic rate as measured by indirect calorimetry is increased. The prevalence of thyroid peroxidase (TpO) antibodies and thyroid-stimulating immunoglobulins (TSIs) is similar to that of the normal population. Specific anti-TSH receptor autoantibodies have been detectable in 4% of patients who later developed Graves disease [94,107]. If TPP is suspected, the differential diagnosis of familial periodic paralysis can be excluded on the basis of a positive family history or abnormal muscle fiber conduction velocity in the latter disease [102].

If MRI studies of the pituitary gland are equivocal, the differential diagnosis between a TSH-secreting tumor and resistance to thyroid hormone (RTH) should be determined [108], necessitating dynamic testing with TRH or octreotide. In patients harboring TSH-secreting pituitary adenomas, the TSH response to TRH administration (200–500 μg intravenously) is absent or blunted in approximately 90% of patients, regardless of previous thyroid ablation [94]. The unresponsiveness to TRH has been attributed to the lack of TRH receptors on these adenomas [109]. Native

somatostatin or its analogues inhibit TSH secretion in most patients harboring TSH adenomas and may be predictive of the efficacy of long-term treatment in up to 94% of patients [110]. The α-subunit response to these stimulatory agents usually parallels that of TSH [111]. RTH can be diagnosed based on the documentation of familial cases; TSH level and α-subunit serum level, which are frequently in the normal range; SHBG in the normal range, except in RTH patients on estrogen therapy or those showing profound hypogonadism; an intact or increased response of TSH to TRH, with a peak level 20 minutes after TRH administration [112,113]; and an absent or mild TSH response to octreotide [96]. In difficult cases, particularly after thyroidectomy, genetic investigations for RTH may be required for diagnostic purposes [108].

Bilateral petrosal sinus sampling has been used in difficult cases, allowing for the identification and lateralization of a microadenoma not seen on radiographic scans [114]. Pituitary scintigraphy with radiolabeled Tyr^3-substituted octreotide and ^{111}In-octreotide tomography have been shown to image somatostatin receptors successfully on thyrotropinomas [115,116]. Tumor size reduction after treatment with octreotide did not, however, correlate significantly with tumor receptor labeling [116].

References

[1] Kunwar S, Wilson CB. Pediatric pituitary adenomas. J Clin Endocrinol Metab 1999;84:4385–9.

[2] Terada T, Kovacs K, Stefaneanu L, et al. Incidence, pathology, and recurrence of pituitary adenomas: study of 647 unselected surgical cases. Endocr Pathol 1995;6:301–10.

[3] Wenig BM, Heffess CS, Adair CF. Neoplasms of the pituitary gland. In: Wenig BM, Heffess CS, Adair CF, editors. Atlas of endocrine pathology. 1st edition. Philadelphia: WB Saunders; 1997. p. 11–29.

[4] Burgess JR, Sheperd JJ, Parameswaran V, et al. Spectrum of pituitary disease in multiple endocrine neoplasia type 1 (MEN 1): clinical, biochemical, and radiological features of pituitary disease in a large MEN 1 kindred. J Clin Endocrinol Metab 1996;81:2642–6.

[5] Jeffcoat WJ, Pound N, Sturrock NDC, et al. Long-term follow-up of patients with hyperprolactinaemia. Clin Endocrinol 1996;45:299–303.

[6] Molitch ME. Disorders of prolactin secretion. Endocrinol Metab Clin North Am 2001;30: 585–609.

[7] Weiss MH, Teal J, Gott P, et al. Natural history of microprolactinomas: six-year follow-up. Neurosurgery 1983;12:180–3.

[8] Faglia G. Prolactinomas and hyperprolactinemic syndrome. In: DeGroot LJ, Jameson JL, editors. Endocrinology. 4th edition. Philadelphia: WB Saunders; 2001. p. 329–42.

[9] Greenman Y, Tordjman K, Stern N. Increased body weight associated with prolactin secreting pituitary adenomas: weight loss with normalization of prolactin. Clin Endocrinol 1998;48:547–53.

[10] Barkan AL, Chandler WF. Giant pituitary prolactinoma with falsely low serum prolactin: the pitfall of the "high-dose hock effect": case report. Neurosurgery 1998;42:913–6.

[11] Petakov MS, Damjanovic SS, Nikolic-Durovic MM, et al. Pituitary adenomas secreting large amounts of prolactin may give false low values in immunoradiometric assays. The hook effect. J Endocrinol Invest 1998;21:184–8.

[12] St-Jean J, Blain F, Comtois R. High prolactin levels may be missed by immunoradiometric assay in patients with macroprolactinomas. Clin Endocrinol 1996;44:305–9.

[13] Rand T, Kink E, Sator M, et al. MRI of microadenomas in patients with hyperprolactinaemia. Neuroradiology 1996;38:744–6.

[14] Molithc ME. Pituitary incidentilomas. Endocrinol Metab Clin North Am 1997;26:725–39.

[15] Young WF Jr, Scheithauer BW, Kovacs KT, et al. Gonadotroph adenoma of the pituitary gland: a clinicopathologic analysis of 100 cases. Mayo Foundation for Medical Education and Research 1996;71:649–56.

[16] Snyder PJ. Gonadotroph adenomas. In: DeGroot LJ, Jameson JL, editors. Endocrinology. Philadelphia: WB Saunders; 2001. p. 313–20.

[17] Greenman Y, Melmed S. Diagnosis and management of nonfunctioning pituitary tumors. Annu Rev Med 1996;47:95–106.

[18] Christin-Maitre S, Rongieres-Bertrand C, Kottler M-L, et al. Clinical case seminar. A spontaneous and severe hyperstimulation of the ovaries revealing a gonadotroph adenoma. J Clin Endocrinol Metab 1998;83:3450–3.

[19] Abrosi B, Basseti M, Ferrario R, et al. Precocious puberty in a boy with a PRL-, LH-, and FSH-secreting pituitary tumour: biosynthetic characterization and clinical studies. Acta Endocrinol 1990; 122:569–76.

[20] Faggiano M, Criscuolo T, Perrone I, et al. Sexual precocity in a boy due to hypersecretion of LH and prolactin by a pituitary adenoma. Acta Endocrinol 1983;102:167–72.

[21] Katznelson L, Alexander JM, Klibanski A. Clinically nonfunctioning pituitary adenomas. J Clin Endocrinol Metab 1993;76:1089–94.

[22] Daneshdoost L, Gennarelli TA, Bashey HM, et al. Recognition of gonadotroph adenomas in women. N Engl J Med 1991;324:589–94.

[23] Daneshdoost L, Gennarelli TA, Bashey HM, et al. Identification of gonadotroph adenomas in men

with clinically nonfunctioning adenomas by the luteinizing hormone β subunit response to thyrotropin-releasing hormone. J Clin Endocrinol Metab 1993;77:1352–5.
[24] Maroldo TV, Dillon WP, Wilson CB. Advances in diagnostic techniques of pituitary tumors and prolactinomas. Curr Opin Oncol 1992;4: 105–15.
[25] De Herder WW, Reijs AEM, Kwekkeboom DJ, et al. In vivo imaging of pituitary tumours using a radiolabelled dopamine D2 receptor radioligand. Clin Endocrinol 1996;45:755–67.
[26] Ferone D, Lastoria S, Colao A, et al. Correlation of scintigraphic results using ^{123}I-methoxybenzamide with hormone levels and tumor size response to quinagolide in patients with pituitary adenomas. J Clin Endocrinol Metab 1998;83:248–52.
[27] Oppizi G, Cozzi R, Dallabonzana D, et al. Scintigraphic imaging of pituitary adenomas: an in vivo evaluation of somatostatin receptors. J Endocrinol Invest 1998;21:512–9.
[28] Plockinger U, Reichel M, Fett U, et al. Preoperative octreotide treatment of growth hormone-secreting and clinically nonfunctioning pituitary macroadenomas: effect on tumor and lack of correlation with immunohistochemistry and somatostatin receptor scintigraphy. J Clin Endocrinol Metab 1994;79:1416–23.
[29] Holdaway IM, Rajasoorya C. Epidemiology of acromegaly. Pituitary 1999;2:29–41.
[30] Abe T, Tara LA, Ludecke DK. Growth hormone-secreting pituitary adenomas in childhood and adolescence: features and results of transnasal surgery. Neurosurgery 1999;45:1–10.
[31] Cheung NW, Boyages SC. Increased incidence of neoplasia in females with acromegaly. Clin Endocrinol 1997;47:323–7.
[32] Colao A, Cuocolo A, Marzullo P. Impact of patient's age and disease duration on cardiac performance in acromegaly: a radionuclide angiography study. J Clin Endocrinol Metab 1999;84: 1518–23.
[33] Jenkins PJ, Fairclough PD, Richards T, et al. Acromegaly, colonic polyps and carcinoma. Clin Endocrinol 1997;47:17–22.
[34] Minniti G, Jaffrain-Rea ML, Moroni C, et al. Echocardiographic evidence for a direct effect of GH/IGF-1 hypersecretion on cardiac mass and function in young acromegalics. Clin Endocrinol 1998;49:101–6.
[35] Ozbey N, Oncul A, Bugra Z, et al. Acromegalic cardiomyopathy: evaluation on the left ventricular diastolic function in the subclinical stage. J Endocrinol Invest 1997;20:305–11.
[36] Ben-Shlomo A, Melmed S. Acromegaly. Endocrinol Metab Clin North Am 2001;30:565–81.
[37] Schulz S, Redlich A, Koppe I, et al. Carney complex—an unexpected finding during puerperium. Gynecol Obstet Invest 2001;51:211–3.
[38] Orme SM, McNally RJQ, Cartwright RA, et al. Mortality and cancer incidence in acromegaly: a retrospective cohort study. J Clin Endocrinol Metab 1998;83:2730–4.
[39] Cannavo S, Squadrito S, Finocchiaro MD, et al. Goiter and impairment of thyroid function in acromegalic patients: basal evaluation and follow-up. Horm Metab Res 2000;32:190–5.
[40] Coalo A, Marzullo P, Gianfranco V, et al. Reversibility of joint thickening in acromegalic patients: an ultrasonography study. J Clin Endocrinol Metab 1993;77:1352–5.
[41] Coalo A, Marzullo P, Spiezia S, et al. Effect of growth hormone (GH) and insulin-like growth factor I on prostate diseases: an ultrasonographic and endocrine study in acromegaly, GH deficiency, and healthy subjects. J Clin Endocrinol Metab 1999;84:1986–91.
[42] Colao A, Merola B, Ferone D, et al. Extensive personal experience. Acromegaly. J Clin Endocrinol Metab 1997;82:2777–81.
[43] Grunstein RR, Ho KY, Sullivan CE, et al. Sleep apnea in acromegaly. Ann Intern Med 1991;115: 527–32.
[44] Isono S, Saeke N, Tanaka A, et al. Collapsibility of passive pharynx in patients with acromegaly. Am J Respir Care Med 1999;160:64–8.
[45] Longobardi S, Di Somma C, Di Rella F, et al. Bone mineral density and circulating cytokines in patients with acromegaly. J Endocrinol Invest 1998;21:688–93.
[46] Patel YC, Ezzat S, Chick CL, et al. Guidelines for the diagnosis and treatment of acromegaly: a Canadian perspective. Clin Invest Med 2000;23: 172–87.
[47] Perkins AT, Morgenlander JC. Endocrinologic causes of peripheral neuropathy. Postgrad Med 1997;102:81–106.
[48] Quabbe H-J, Plockinger U. Metabolic aspects of acromegaly and its treatment. Metabolism 1996; 45:61–2.
[49] Russel-Jones DL, Weissberger AJ, Bowes SB, et al. The effect of growth hormone on protein metabolism in adult growth hormone deficient patients. Clin Endocrinol (Oxf) 1993;38:427–31.
[50] Sacca L, Cittadini A, Colao A, et al. Growth hormone and the heart. Endocr Rev 1994;15: 555–73.
[51] Trotman-Dickenson B, Weetman AP, Hughes JMB, et al. Upper airflow obstruction and pulmonary function in acromegaly: relationship to disease activity. Q J Med 1991;79:527–33.
[52] Balkany C, Cushing GW. An association between acromegaly and thyroid carcinoma. Thyroid 1995; 5:47–50.
[53] Jenkins PJ, Frajese V, Jones A-M, et al. Insulin-like growth factor I and the development of colorectal neoplasia in acromegaly. J Clin Endocrinol Metab 2000;85:3218–21.

[54] Rajasoorya C, Holdawy M, Wrightson P, et al. Determinants of clinical outcome and survival in acromegaly. Clin Endocrinol 1994;41:95–102.
[55] Lie JT, Grossman ST. Pathology of the heart in acromegaly: anatomic findings in 27 autopsied patients. Am Heart J 1980;100:41–52.
[56] Randall RV, Scheithauer BW, Laws ER Jr, et al. Pituitary adenomas associated with hyperprolactinemia: a clinical and immunohistochemical study of 97 patients operated on transsphenoidally. Mayo Clin Proc 1985;60:753–62.
[57] Tendall H, Wales JK. Primary hyperthyroidism occurring in association with acromegaly. Br J Clin Pract 1989;43:177–9.
[58] Cats A, Dullaart R, Kleibeuker JH, et al. Increased epithelial cell proliferation in the colon of patients with acromegaly. Cancer Res 1996;56:523–6.
[59] Ezzat S, Strom C, Melmed S. Colon polyps in acromegaly. Ann Intern Med 1991;114:754–5.
[60] Furman K, Ezzat S. Psychological features of acromegaly. Psychother Psychosom 1998;67:147–53.
[61] Herman-Bonert V, Seliverstov M, Melmed S. Pregnancy in acromegaly: successful therapeutic outcome. J Clin Endocrinol Metab 1998;83:727–31.
[62] Lee Vance M. Endocrinological evaluation of acromegaly. J Neurosurg 1998;89:499–500.
[63] Melmed S. Evaluation of pituitary masses. In: DeGroot LJ, Jameson JL, editors. Endocrinology. 4th edition. Philadelphia: WB Saunders; 2001. p. 282–8.
[64] Guistina A, Barkan A, Casanueva F, et al. Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 2000;85:526–9.
[65] Jasper H, Pennisi P, Vitale M, et al. Evaluation of disease activity by IGF-1 and IGF binding protein-3 (IGFBP3) in acromegalic patients distributed according to a clinical score. J Endocrinol Invest 1999;22:29–34.
[66] Freda PU, Post KD, Powell JS, et al. Evaluation of disease status with sensitive measures of growth hormone secretion in 60 postoperative patients with acromegaly. J Clin Endocrinol Metab 1998; 83:3808–16.
[67] Meir CA, Biller BMK. Clinical and biochemical evaluation of Cushing's syndrome. Endocrinol Metab Clin North Am 1997;26:741–62.
[68] Belsky JL, Cuello B, Swanson LW, et al. Cushing's syndrome due to ectopic production of corticotropin-releasing factor. J Clin Endocrinol Metab 1985;60:496–500.
[69] Schteingart DE, Lloyd RV, Akil H, et al. Cushing's syndrome secondary to ectopic corticotropin-releasing hormone-adrenocorticotropin secretion. J Clin Endocrinol Metab 1986;63:770–5.
[70] Nieman LK. Cushing's syndrome. In: DeGroot LJ, Jameson JL, editors. Endocrinology. 4th edition. Philadelphia: WB Saunders; 2001. p. 1691–15.
[71] Jones KL. The Cushing syndromes. Pediatr Clin North Am 1990;37:1313–32.
[72] Della CS, Corsello SM, Satta MA, et al. Intracranial and spine dissemination of an ACTH secreting pituitary neoplasia. Case report and review of the literature. Ann Endocrinol (Paris) 1997;58:503–9.
[73] Young WF, Scheithauer BW, Gharib H, et al. Cushing's syndrome due to primary multinodular corticotrope hyperplasia. Mayo Clin Proc 1988; 63:256–62.
[74] Findling JW, Raff H. Diagnosis and differential diagnosis of Cushing's syndrome. Endocrinol Metab Clin North Am 2001;30:729–45.
[75] Shapiro MS, Shenkman L. Variable hormonogenesis in Cushing's syndrome. Q J Med 1990;79: 351–63.
[76] Mengden T, Habmann P, Mullen J, et al. Urinary free cortisol versus 17-hydroxycorticosteroids: a comparative study of their diagnostic value in Cushing's syndrome. Clin Invest 1992;70:545–8.
[77] Newell-Price J, Trainer P, Besser M, et al. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. Endocr Rev 1998;19:647–72.
[78] Tsigos C, Chrousos GP. Differential diagnosis and management of Cushing's syndrome. Annu Rev Med 1996;47:443–61.
[79] Gorges R, Knappe G, Gerl H, et al. Diagnosis of Cushing's syndrome: re-evaluation of midnight plasma cortisol vs urinary free cortisol and low-dose dexamethasone suppression test in a large patient group. J Endocrinol Invest 1999;22:241–9.
[80] Aron DC. Diagnostic implications of adrenal physiology and clinical epidemiology for evaluation of glucocorticoid excess and deficiency. In: DeGroot LJ, Jameson JL, editors. Endocrinology. 4th edition. Philadelphia: WB Saunders; 2001. p. 1655–70.
[81] Findling JW. Clinical application of a new immunoradiometric assay for ACTH. Endocrinologist 1992;2:360–5.
[82] Streeten DHP, Fas FH, Elders MJ, et al. Hypercortisolism in childhood: shortcomings of conventional diagnostic criteria. Pediatrics 1975;56: 797–803.
[83] Nieman LK, Oldfield EH, Wesley R, et al. A simplified morning ovine corticotropin-releasing hormone stimulation test for the differential diagnosis of ACTH-dependent Cushing syndrome. J Clin Endocrinol Metab 1993;77:1308–12.
[84] Doppman JL, Frank JA, Dwyer AJ, et al. Gadolinium DTPA enhanced imaging of ACTH-secreting microadenomas of the pituitary gland. J Comput Assist Tomogr 1988;12:728–35.
[85] Bonelli FS, Huston J, Carpenter PC, et al. Adrenocorticotropic hormone-dependent Cushing's syndrome: sensitivity and specificity of inferior petrosal sinus sampling. AJNR Am J Neuroradiol 2000;21:690–6.
[86] Findling JW, Kehoc ME, Shaker JL, et al. Routine inferior petrosal sinus sampling in the differential

diagnosis of ACTH-dependent Cushing's syndrome: early recognition of the occult ectopic ACTH syndrome. J Clin Endocrinol Metab 1991; 73:408–13.
[87] Findling JW, Raff H. Newer diagnostic techniques and problems in Cushing's disease. Endocrinol Metab Clin North Am 1999;28:191–210.
[88] Invitti C, Giraldi FP, de Martin M, et al. Inferior petrosal sinus sampling in patients with Cushing's syndrome and contradicting response to dynamic testing. Clin Endocrinol 1999;51:255–7.
[89] Kaltsas GA, Giannulis MG, Newell-Price JDC, et al. A critical analysis of the value of simultaneous inferior petrosal sinus sampling in Cushing's disease and the occult ectopic adrenocorticotropin syndrome. J Clin Endocrinol Metab 1999; 84:487–92.
[90] Landlot AM, Schubiger O, Maurer R, et al. The value of inferior petrosal sinus sampling in diagnosis and treatment of Cushing's disease. Clin Endocrinol (Oxf) 1994;40:485–92.
[91] Blevins LS Jr, Clark RV, Owens DS. Thromboembolic complications after inferior petrosal sinus sampling in patients with Cushing's syndrome. Endocr Pract 1998;4:365–7.
[92] Doppman JL, Nieman LK, Chang R, et al. Selective venous sampling from the cavernous sinuses is not a more reliable technique than sampling from the inferior petrosal sinuses in Cushing's syndrome. J Clin Endocrinol Metab 1995;80:2485–9.
[93] Doppman JL, Oldfield EH, Nieman LK. Bilateral sampling of the internal jugular vein to distinguish between mechanisms of adrenocorticotropic hormone-dependent Cushing's syndrome. Ann Intern Med 1998;128:33–6.
[94] Beck-Peccoz P, Bruckner-Davis F, Persani L, et al. Thyrotropin-secreting pituitary tumors. Endocr Rev 1996;17:610–38.
[95] Bertholon-Gregoire M, Trouillas J, Guigard MP, et al. Mono- and plurihormonal thyrotropic pituitary adenomas: pathological, hormonal and clinical studies in 12 patients. Eur J Endocrinol 1999;140:519–27.
[96] Bruckner-Davis F, Oldfield EH, Skarulis MC, et al. Thyrotropin-secreting pituitary tumors: diagnostic criteria, thyroid hormone sensitivity, and treatment outcome in 25 patients followed at the National Institutes of Health. J Clin Endocrinol Metab 1999;84:476–86.
[97] Shomali ME, Katznelson L. Medical therapy for gonadotroph and thyrotroph tumors. Endocrinol Metab Clin North Am 1999;28:223–40.
[98] Burgess JR, Shepherd JJ, Greenaway TM. Thyrotropinomas in multiple endocrine neoplasia type 1 (MEN-1). Aust NZ J Med 1994;24:740–1.
[99] Gessl A, Freissmuth M, Czech T, et al. Growth hormone-prolactin thyrotropin-secreting pituitary adenoma in atypical McCune-Albright syndrome with functionally normal Gs∝protein. J Clin Endocrinol Metab 1994;79:1128–34.
[100] Chiovalo L, Barbesino G, Pinchera A. Graves' disease. In: DeGroot LJ, Jameson JK, editors. Endocrinology. 4th edition. Philadelphia: WB Saunders; 2001. p. 1422–49.
[101] Calle-Pascual AL, Yuste E, Martin P, et al. Association of a thyrotropin-secreting pituitary adenoma and a thyroid follicular carcinoma. J Endocrinol Invest 1991;14:499–502.
[102] Alings AMW, Fliers E, deHerder WW, et al. A thyrotropin-secreting pituitary adenoma as a cause of thyrotoxic periodic paralysis. J Endocrinol Invest 1998;21:703–6.
[103] Beck-Peccoz P, Persani L, Mantovani S, et al. Thyrotropin-secreting pituitary adenomas. Metabolism 1996;45:75–9.
[104] Spencer CA, Takeuchi M, Kazarosyan M. Current status and performance goals for serum TSH assays. Clin Chem 1996;42:140–5.
[105] Gesundheit N, Petrick PA, Nissim M, et al. Thyrotropin-secreting pituitary adenomas. Clinical and biochemical heterogeneity. Case reports and follow-up of nine patients. Ann Intern Med 1989; 111:827–35.
[106] Beck-Peccoz P, Persani L, Faglia G. Glycoprotein hormone ∝-subunit in pituitary adenomas. Trends Endocrinol Metab 1992;3:41–5.
[107] Kamoi K, Mitsuma T, Sato H, et al. Hyperthyroidism caused by a pituitary thyrotropin-secreting tumor with excessive secretion of thyrotropin-releasing hormone and subsequently followed by Graves disease in a middle-aged woman. Acta Endocrinol (Copenh) 1985;110:373–82.
[108] Faglia G, Beck-Peccoz P, Piscitelli G, et al. Inappropriate secretion of thyrotropin by the pituitary. Horm Res 1987;26:79–99.
[109] Spada A, Bassetti M, Martino E, et al. *In vitro* studies on TSH secretion and adenylate cyclase activity in a human TSH-secreting pituitary adenoma. Effects of somatostatin and dopamine. J Endocrinol Invest 1985;8:193–8.
[110] Chanson P, Weintraub BD, Harris AG. Octreotide therapy for thyroid stimulating-secreting pituitary adenomas. A follow-up of 52 patients. Ann Intern Med 1993;119:236–40.
[111] Losa M, Giovanelli M, Persani L, et al. Criteria of cure and follow-up of central hyperthyroidism due to thyrotropin-secreting pituitary adenomas. J Clin Endocrinol Metab 1996;81:3086–90.
[112] Bruckner-Davis F, Skarulis MC, Grace MB, et al. Genetic and clinical features of 42 kindreds with RTH. The NIH prospective study. Ann Intern Med 1995;123:572–83.
[113] Refetoff S, Weiss RE, Usala SJ. The syndrome of resistance to thyroid hormone. Endocr Rev 1993; 14:348–99.
[114] Frank SJ, Gesundheit N, Doppman JL, et al. Preoperative lateralization of pituitary microadenomas

by petrosal sinus sampling: utility in two patients with non-ACTH-secreting tumors. Am J Med 1989; 87:679–82.

[115] Lamberts SWJ, Krenning EP, Reubi J-C. The role of somatostatin and its analogs in the diagnosis and treatment of tumors. Endocr Rev 1991;12:450–82.

[116] Verhoeff NPLG, Bemelman FJ, Wiersinga WM, et al. Imaging of dopamine D2 and somatostatin receptors in vivo using single-photon emission tomography in a patient with a TSH/PRL-producing pituitary macroadenoma. Eur J Nucl Med 1993;20:555–61.