TABLE 403-7 CLINICAL FEATURES OF CUSHING'S SYNDROME (ALL AGES)

Symptoms/Signs	Frequency, %
Obesity or weight gain (>115% ideal body weight)	80
Thin skin	80
Moon facies	75
Hypertension	75
Purple skin striae	65
Hirsutism	65
Menstrual disorders (usually amenorrhea)	60
Plethora	60
Abnormal glucose tolerance	55
Impotence	55
Proximal muscle weakness	50
Truncal obesity	50
Acne	45
Bruising	45
Mental changes	45
Osteoporosis	40
Edema of lower extremities	30
Hyperpigmentation	20
Hypokalemic alkalosis	15
Diabetes mellitus	15

Source: Adapted from MA Magiokou et al, in ME Wierman (ed): *Diseases of the Pituitary.* Totowa, NJ, Humana, 1997.

be used to identify patients with hypercortisolism. As nadir levels of cortisol occur at night, elevated midnight serum or salivary samples of cortisol are suggestive of Cushing's syndrome. Basal plasma ACTH levels often distinguish patients with ACTH-independent (adrenal or exogenous glucocorticoid) from those with ACTH-dependent (pituitary, ectopic ACTH) Cushing's syndrome. Mean basal ACTH levels are about eightfold higher in patients with ectopic ACTH secretion than in those with pituitary ACTH-secreting 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 sensitivity 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 403-8)**. 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. 406.**

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 distinguish 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 in the diagnosis of peripheral circulation provides a strategy for confirming and localizing pituitary ACTH production. Sampling is performed at baseline and 2, 5, and 10 min after intravenous bovine CRH (1 μg/kg) injection. An increased ratio (>2) of inferior petrosal:peripheral vein ACTH confirms pituitary Cushing's syndrome. After CRH injection, peak petrosal:peripheral ACTH ratios ≥3 confirm the presence of a pituitary ACTH-secreting tumor. 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 about 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.

TABLE 403-8 DIFFERENTIAL DIAGNOSIS OF ACTH-DEPENDENT CUSHING'S SYNDROME[a]

	ACTH-Secreting Pituitary Tumor	Ectopic ACTH Secretion
Etiology	Pituitary corticotrope adenoma	Bronchial, abdominal carcinoid
	Plurihormonal adenoma	Small cell lung cancer
		Thymoma
Sex	F > M	M > F
Clinical features	Slow onset	Rapid onset
		Pigmentation
		Severe myopathy
Serum potassium <3.3μg/L	<10%	75%
24-h urinary free cortisol (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%	10%
	Macroadenomas: 50%	
Inferior petrosal sinus sampling (IPSS)		
Basal		
IPSS: peripheral	>2	<2
CRH-induced		
IPSS: peripheral	>3	<3

[a]ACTH-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.

TREATMENT CUSHING'S SYNDROME

Selective transsphenoidal resection is the treatment of choice for Cushing's disease **(Fig. 403-6)**. The remission rate for this procedure is ~80% for microadenomas but <50% for macroadenomas. However, surgery is rarely successful when the adenoma is not visible on MRI. After successful tumor resection, most patients experience a postoperative period of symptomatic ACTH deficiency that may last up to 12 months. This usually requires low-dose cortisol replacement, as patients experience both steroid withdrawal symptoms and have a suppressed hypothalamic-pituitary-adrenal axis. Biochemical recurrence occurs in approximately 5% of patients in whom surgery was initially successful.

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 fertility are less important, hemi- or total hypophysectomy may be necessary if a discrete pituitary adenoma is not recognized. Pituitary irradiation may be used after unsuccessful surgery, but it cures only about 15% of patients. Because the effects of radiation are slow and only partially effective in adults, steroidogenic inhibitors are used in combination with pituitary irradiation to block adrenal effects of persistently high ACTH levels.

Pasireotide (600 or 900 ug/day subcutaneously), a somatostatin analog with high affinity for SST5 > SST2 receptors, has been approved for treating patients with ACTH-secreting pituitary tumors when surgery is not an option or has been unsuccessful. In clinical trials, the drug lowered plasma ACTH levels, normalized 24-h urinary free cortisol levels in about 25% of patients, and resulted in up to 40% mean pituitary tumor shrinkage. Side effects include development of