Corticotropin (ACTH)-releasing hormone (CRH) is synthesized in the hypothalamus and carried to the anterior pituitary in the portal system. CRH stimulates ACTH release from the anterior pituitary, which in turn stimulates the adrenal cortex to secrete cortisol (hypothalamic-pituitary-adrenal or HPA axis).\textsuperscript{1}–\textsuperscript{4} Cortisol inhibits the synthesis and secretion of both CRH and ACTH in a negative feedback regulation system. In Cushing syndrome, the HPA axis has lost its ability for self-regulation, due to excessive secretion of either ACTH or cortisol and the loss of the negative feedback function. Diagnostic tests, on the other hand, take advantage of the tight regulation of the HPA axis in the normal state and its disturbance in Cushing syndrome to guide therapy toward the primary cause of this disorder.
Cushing syndrome is a rare entity, especially in children.\(^1\) The overall incidence of Cushing syndrome is approximately 2 to 5 new cases per million people per year. Only approximately 10% of the new cases each year occur in children. As in adult patients, in children with Cushing syndrome there is a female-to-male predominance, which decreases with younger age. There might even be a male-to-female predominance in infants and young toddlers with Cushing syndrome.\(^1,3,4\) The most common cause of Cushing syndrome in children is exogenous or iatrogenic Cushing syndrome. This is the result of chronic administration of glucocorticoids or ACTH. Glucocorticoids are being used more frequently for the treatment of many nonendocrine diseases including pulmonary, autoimmune, dermatologic, hematologic, and neoplastic disorders. In addition, ACTH is being used for the treatment of certain seizure disorders. The most common cause of endogenous Cushing syndrome in children is ACTH overproduction from the pituitary called Cushing disease. It is usually caused by an ACTH-secreting pituitary microadenoma and, rarely, a macroadenoma. ACTH secretion occurs in a semiautonomous manner, maintaining some of the feedback of the HPA axis. Cushing disease accounts for approximately 75% of all cases of Cushing syndrome in children over 7 years. In children under 7 years, Cushing disease is less frequent; adrenal causes of Cushing syndrome (adenoma, carcinoma, or bilateral hyperplasia) are the most common causes of the condition in infants and young toddlers. Ectopic ACTH production occurs rarely in young children; it also accounts for less than 1% of the cases of Cushing syndrome in adolescents. Sources of ectopic ACTH include small cell carcinoma of the lung, carcinoid tumors in the bronchus, pancreas, or thymus; medullary carcinomas of the thyroid, pheochromocytomas; and other neuroendocrine tumors, especially those of the pancreas and gut carcinoids. Rarely, ACTH overproduction by the pituitary may be the result of CRH oversecretion by the hypothalamus or by an ectopic CRH source. However, this cause of Cushing syndrome has only been described in a small number of cases, and never in young children. Its significance lies in the fact that diagnostic tests that are usually used for the exclusion of ectopic sources of Cushing syndrome have frequently misleading results in the case of CRH-induced ACTH oversecretion. Autonomous secretion of cortisol from the adrenal glands, or ACTH-independent Cushing syndrome, accounts for approximately 15% of all the cases of Cushing syndrome in childhood. However, although adrenocortical tumors are rare in older children, in younger children they are more frequent. In prepubertal children, adrenocortical lesions are the most frequent cause of Cushing syndrome. Adrenocortical neoplasms account for 0.6% of all childhood tumors; Cushing syndrome is a manifestation of approximately one-third of all adrenal tumors.\(^3-5\) In young children, unilateral (single) adrenal tumors presenting with Cushing syndrome are often malignant (more than 70%). Most patients present under age 5, contributing thus to the first peak of the known bimodal distribution of adrenal cancer across the life span. As in adults, there is a female-to-male predominance. The tumors usually occur unilaterally; however, in 2% to 10% of patients they occur bilaterally. Recently, bilateral nodular adrenal disease has been appreciated as a more frequent than previously thought cause of Cushing syndrome in childhood.\(^5,6\) Primary pigmented adrenocortical nodular disease (PPNAD) is a genetic disorder with the majority of cases associated with Carney complex, a syndrome of multiple endocrine gland abnormalities in addition to lentigines and myxomas. The adrenal glands in PPNAD are most commonly normal or even small in size, with multiple pigmented nodules usually (but not always) surrounded by an atrophic cortex. The nodules are autonomously functioning, resulting in the surrounding atrophy of the cortex. Children
and adolescents with PPNAD frequently have periodic, cyclical, or otherwise atypical Cushing syndrome. Massive macronodular adrenal hyperplasia (MMAD) is another rare bilateral disease that leads to Cushing syndrome. The adrenal glands are massively enlarged, with multiple, huge nodules that are typical yellow-to-brown cortisol-producing adenomas. Most cases of MMAD are sporadic, although a few familial cases have been described; in those cases, the disease appears in children. In some patients with MMAD, cortisol levels appear to increase with food ingestion (food-dependent Cushing syndrome). These patients have an aberrant expression of the gastric inhibitory polypeptide receptor (GIPR) in the adrenal glands. In the majority of patients with MMAD, however, the disease does not appear to be GIPR-dependent; aberrant expression of other receptors may be responsible for the disease in these patients. Adrenal adenomas or, more frequently, bilateral macronodular adrenal hyperplasia can also be seen in McCune Albright syndrome (MAS). In this syndrome, there is a somatic mutation of the GNAS1 gene leading to constitutive activation of the Gsα protein and continuous, non-ACTH-dependent activation of steroidogenesis by the adrenal cortex. Cushing syndrome in MAS is rare and usually presents in the infantile period (before 6 months of age); interestingly, a few children have had spontaneous resolution of their Cushing syndrome. Aberrant cyclic adenosine monophosphate (cAMP) signaling has been linked to almost all genetic forms of adrenal-dependent cortisol excess. PPNAD is associated with germline inactivating mutations of the PRKAR1A gene. Several other forms of micronodular bilateral adrenocortical hyperplasia (BAH) are not associated with inactivating mutations of the PRKAR1A gene, but may occur as de novo or autosomal-dominant inheritance of mutations, in the PDE11A or PDE8B genes. Among functional pituitary tumors in early childhood, ACTH-producing adenomas are probably the most common, although they are still considerably rare. To date, no genetic defects have been consistently associated with childhood corticotropinomas, which only rarely occur in the familial setting, and then, most commonly in the context of multiple endocrine neoplasia type 1 (MEN 1) and rarely due to AIP mutations.

**CLINICAL PRESENTATION**

In most children, the onset of Cushing syndrome is insidious. The most common presenting symptom is weight gain; in childhood, lack of height gain consistent with the weight gain is the most common presentation of Cushing syndrome. A typical growth chart for a child with Cushing syndrome is shown in Fig. 1. Other common problems reported in children include facial plethora, headaches, hypertension, hirsutism, amenorrhea, and delayed sexual development. Pubertal children may present with virilization. Skin manifestations, including acne, violaceous striae, bruising, and acanthosis nigricans are also common. Compared with adult patients with Cushing syndrome, symptoms that are less commonly seen in children include sleep disruption, muscular weakness, and problems with memory.

**DIAGNOSTIC GUIDELINES**

The appropriate therapeutic interventions in Cushing syndrome depend on accurate diagnosis and classification of the disease. The medical history and clinical evaluation, including review of growth data, are important to make the initial diagnosis of Cushing syndrome. Upon suspicion of Cushing syndrome, laboratory and imaging confirmations are necessary. An algorithm of the diagnostic process is presented in Fig. 2.
The first step in the diagnosis of Cushing syndrome is to document hypercortisolism, which is typically done in the outpatient setting. Because of the circadian nature of cortisol and ACTH, isolated cortisol and ACTH measurements are not of great value in diagnosis. One excellent screening test for hypercortisolism is a 24-hour urinary free cortisol (UFC) excretion (corrected for body surface area). However, it is often difficult to obtain a 24-hour urine collection reliably in the outpatient setting, particularly in the pediatric population. Falsely high UFC may be obtained because of physical and emotional stress, chronic and severe obesity, pregnancy, chronic exercise, depression, poor diabetes control, alcoholism, anorexia, narcotic withdrawal, anxiety, malnutrition, and high water intake. These conditions may cause sufficiently high UFCs to cause what is known as pseudo-Cushing syndrome. On the other hand, falsely low UFC may be obtained mostly with inadequate collection.

Another baseline test for the establishment of the diagnosis of Cushing syndrome is a low-dose dexamethasone suppression test. This test involves giving 1 mg of
Dexamethasone at 11 and measuring a serum cortisol level the following morning at 8 AM. If the serum cortisol level is greater than 1.8 μg/dL, further evaluation is necessary. This test has a low percentage of false-normal suppression; however, the percentage of false positives is higher (approximately 15% to 20%). It should be remembered that the 1 mg overnight test, like the 24-hour UFCs, does not distinguish between hypercortisolism from Cushing syndrome and other hypercortisolemic states. If the response to the 1 mg dexamethasone overnight suppression test and the 24-hour UFC are both normal, a diagnosis of Cushing syndrome may be excluded with the following caveat: 5% to 10% of patients may have intermittent or periodic cortisol hypersecretion and may not manifest abnormal results to either test. If periodic or intermittent Cushing syndrome is suspected, continuous follow-up of the patients is recommended, including monitoring of growth and 24-hour UFC. If one of the test results is suggestive of Cushing syndrome, or if there is any question about the diagnosis, then tests that distinguish between pseudo-Cushing syndrome states and Cushing syndrome may be obtained. One such test is the combined dexamethasone-CRH test. In this test, the patient is treated with low-dose dexamethasone (0.5 mg adjusted for weight for children <70 kg) every 6 hours for 8 doses before the administration of CRH (ovine CRH-oCRH) the following morning. ACTH and cortisol levels are measured at baseline (-15, -5, and 0 min) and 15 minutes after the administration of oCRH (plasma dexamethasone level is measured once at baseline). The patient with pseudo-Cushing syndrome will exhibit low or undetectable basal plasma cortisol and ACTH and have a diminished or no response to oCRH stimulation.
Patients with Cushing syndrome will have higher basal cortisol and ACTH levels and will also have a greater peak value with oCRH stimulation. A cortisol level of greater than 1.4 µg/dL (38 nmol/L) 15 minutes after oCRH administration supports a diagnosis of Cushing syndrome, and further evaluation is indicated. However, the author and colleagues recently reported that severe obesity (body mass index [BMI] greater than 2 standard deviations [SD]) confounds the interpretation of the dexamethasone-CRH test. Confirmed height gain is a simple way to help distinguish children with pseudo-Cushing from those with Cushing syndrome. Once the diagnosis of Cushing syndrome is confirmed, there are several tests to distinguish ACTH-dependent disease from the ACTH-independent syndrome.

A spot morning plasma ACTH may be measured; we have recently reported that a cutoff value of 29 pg/mL in children with confirmed Cushing syndrome has a sensitivity of 70% in identifying children with an ACTH-dependent form of the syndrome. It is important to consider the variability in plasma ACTH levels and the instability of the molecule after the sample’s collection. The standard high-dose dexamethasone suppression test (HDDST or Liddle’s test) is used to differentiate Cushing disease from ectopic ACTH secretion and adrenal causes of Cushing syndrome. The Liddle’s test has been modified to giving a high dose of dexamethasone (120 µg/kg, maximum dose 8 mg) at 11 PM and measuring the plasma cortisol level the following morning. We have recently reported in a pediatric population that 20% cortisol suppression from baseline had sensitivity and specificity of 97.5% and 100%, respectively, with the HDDST for differentiating patients with Cushing disease from those with adrenal tumors. Indications for obtaining the classic Liddle’s test, low-dose dexamethasone (30 µg/kg/dose; maximum 0.5 mg/dose) every 6 hours for 8 doses, followed by high-dose dexamethasone (120 µg/kg/dose; maximum 2 mg/dose) every 6 hours for 8 doses (instead of the modified overnight HDDST), include nonsuppression of serum cortisol levels during the HDDST and/or negative imaging studies, and/or suspected adrenal disease. UFC and 17-hydroxysteroid (17OHS) excretion are measured at baseline and after dexamethasone administration during Liddle’s test. Approximately 85% of patients with Cushing disease will have suppression of serum cortisol, UFC, and 17OHS values, whereas less than 10% of patients with ectopic ACTH secretion will have suppression. UFC values should suppress to 90% of baseline value, and 17OHS excretion should suppress to less than 50% of baseline value. This test has been shown to be useful mostly in patients who have suspected adrenal disease; in this case it is used with the aim of identifying a paradoxical stimulation of cortisol secretion, which is found in patients with PPNAD and other forms of BAH, but not in other forms of primary adrenocortical lesions.

We have recently reported in a larger series of pediatric patients that following confirmation of elevated 24-hour UFC (3 collections), a single midnight cortisol value of greater than 4.4 µg/dL followed by a high-dose dexamethasone suppression test (>20% suppression of morning serum cortisol) was the most rapid and accurate way for confirmation and diagnostic differentiation, respectively, of hypercortisolism due to a pituitary or adrenal tumor. However, for accuracy, diurnal testing requires an inpatient stay, and this may limit its use as a routine screening test. An oCRH stimulation test may also be obtained for the differentiation of Cushing disease from ectopic ACTH secretion and/or adrenal lesions. In this test, 85% of patients with Cushing disease respond to oCRH with increased plasma ACTH and cortisol production. Ninety-five percent of patients with ectopic ACTH production do not respond to administration of oCRH. The criterion for diagnosis of Cushing disease is a mean increase of 20% above baseline for cortisol values at 30 and 45 minutes and an increase in the mean corticotropin concentrations of at least 35% over basal value.
at 15 and 30 minutes after CRH administration. When the oCRH and high-dose dexamethasone (Liddle’s or overnight) tests are used together, diagnostic accuracy improves to 98%. The oCRH test should not be used in patients with atypical forms of Cushing syndrome, because individuals with normal pituitary function respond to oCRH like patients with Cushing disease. Interpretation of oCRH testing in the differential diagnosis of Cushing syndrome is only possible when the normal corticotrophs are suppressed by consistently elevated cortisol levels.

Another important tool in the localization and characterization of Cushing syndrome is diagnostic imaging. The most important initial imaging when Cushing disease is suspected is pituitary magnetic resonance imaging (MRI). The MRI should be done in thin sections with high resolution and always with contrast (gadolinium). The latter is important, since only macroadenomas will be detectable without contrast; after contrast, an otherwise normal-looking pituitary MRI might show a hypoenhancing lesion, usually a microadenoma. More than 90% of ACTH-producing tumors are hypoenhancing, whereas only about 5% are hyperenhancing after contrast infusion. However, even with the use of contrast material, pituitary MRI may detect only up to approximately 50% of ACTH-producing pituitary tumors. Recently, the author and colleagues reported that postcontrast spoiled gradient-recalled MRI (SPGR-MRI) was superior to spin echo MRI (SE-MRI) in the detection of a microadenoma in children and adolescents with Cushing disease. Computed tomography (CT) (more preferable than MRI) of the adrenal glands is useful in the distinction between Cushing disease and adrenal causes of Cushing syndrome, mainly unilateral adrenal tumors. The distinction is harder in the presence of bilateral hyperplasia (MMAD or PPNAD) or the rare case of bilateral adrenal carcinoma. Most patients with Cushing disease have ACTH-driven bilateral hyperplasia, and both adrenal glands will appear enlarged and nodular on CT or MRI. Most adrenocortical carcinomas are unilateral and quite large by the time they are detected. Adrenocortical adenomas are usually small, less than 5 cm in diameter, and, like most carcinomas, they involve 1 adrenal gland. MMAD presents with massive enlargement of both adrenal glands, whereas PPNAD is more difficult to diagnose radiologically, because it is usually associated with normal- or small-sized adrenal glands, despite the histologic presence of hyperplasia. A CT or MRI scan of the neck, chest, abdomen, and pelvis may be used for the detection of an ectopic source of ACTH production. Labeled octreotide scanning, positron-emission tomography (PET), and venous sampling may also help in the localization of an ectopic ACTH source.

Since up to 50% of pituitary ACTH-secreting tumors and many of ectopic ACTH tumors may not be detected on routine imaging, and often laboratory diagnosis is not completely clear, catheterization studies must be used to confirm the source of ACTH secretion in ACTH-dependent Cushing syndrome. Bilateral inferior petrosal sinus sampling (IPSS) has been used for the localization of a pituitary microadenoma; however, we have recently reported that it is a poor predictor of the site of a microadenoma in children. In brief, sampling from each inferior petrosal sinus is taken for measurement of ACTH concentration simultaneously with peripheral venous sampling. ACTH is measured at baseline and at 3, 5, and 10 minutes after oCRH administration. Patients with ectopic ACTH secretion have no gradient between either sinus (central) and the peripheral sample. On the other hand, patients with an ACTH-secreting pituitary adenoma have at least a 2-to-1 central-to-peripheral gradient at baseline or 3-to-1 central-to-peripheral gradient after stimulation with oCRH. IPSS is an excellent test for the differential diagnosis between ACTH-dependent forms of Cushing syndrome with a diagnostic accuracy that approximates 100%, as long as it is performed in an experienced clinical center. IPSS, however, may not lead to the
correct diagnosis if it is obtained when the patient is not sufficiently hypercortisolemic or if venous drainage of the pituitary gland does not follow the expected, normal anatomy, or with an ectopic CRH-producing tumor.

**TREATMENT**

The treatment of choice for almost all patients with an ACTH-secreting pituitary adenoma (Cushing disease) is transsphenoidal surgery (TSS). In most specialized centers with experienced neurosurgeons, the success rate of the first TSS is 90% or higher. Treatment failures are most commonly the result of a macroadenoma or a small tumor invading the cavernous sinus. The success rate of repeat TSS is lower, closer to 60%. Postoperative complications include transient diabetes insipidus (DI) and, occasionally, syndrome of inappropriate antidiuretic hormone secretion (SIADH), central hypothyroidism, growth hormone deficiency, hypogonadism, bleeding, infection (meningitis), and pituitary apoplexy. The mortality rate is extremely low, at less than 1%. Permanent pituitary dysfunction (partial or pan-hypopituitarism) and DI are rare but they are more likely after repeat TSS or larger adenomas. Pituitary irradiation is considered an appropriate treatment in patients with Cushing disease following a failed TSS. Up to 80% of patients will have remission after irradiation of the pituitary gland. Hypopituitarism is the most common adverse effect, and it is more frequent when surgery precedes the radiotherapy. The recommended dosage is 4500/5000 cGy total, usually given over a period of 6 weeks. Newer forms of stereotactic radiotherapy are now available as options for treatment of ACTH-secreting pituitary tumors. Photon knife (computer-assisted linear accelerator) or the gamma knife (cobalt –60) approaches are now available; however, experience with these techniques is limited, especially in children. These modalities may be attractive because of the smaller amount of time required for these procedures and the possibility for fewer adverse effects.

The treatment of choice for benign adrenal tumors is surgical resection. This procedure can be done by either transperitoneal or retroperitoneal approaches. In addition, laparoscopic adrenalectomy is also available at many institutions. Adrenal carcinomas may also be surgically resected, unless at later stages. Solitary metastases should be removed, if possible. Therapy with mitotane, which is an adrenocytolytic agent, can be used as an adjuvant therapy or in the case of an inoperable tumor. Other chemotherapeutic options include cisplatin, 5-flourouracil, suramin, doxorubicin, and etoposide. Occasionally glucocorticoid antagonists and steroid synthesis inhibitors are needed to correct the hypercortisolism. Radiotherapy can also be used in the case of metastases. The prognosis for adrenal carcinoma is poor, but usually children have a better prognosis than adults.

Bilateral total adrenalectomy is usually the treatment of choice in bilateral micronodular or macronodular adrenal disease, such as PPNAD and MMAD. In addition, adrenalectomy may be considered as a treatment for those patients with Cushing disease or ectopic ACTH-dependent Cushing syndrome who have either failed surgery or radiotherapy, or their tumor has not been localized, respectively. Nelson syndrome, which includes increased pigmentation, elevated ACTH levels, and a growing pituitary ACTH-producing pituitary tumor, may develop in up to 15% of patients with Cushing disease who are treated with bilateral adrenalectomy. It is possible that children with untreated Cushing disease are especially vulnerable to Nelson syndrome after bilateral adrenalectomy.

Pharmacotherapy is an option in the case of failure of surgery for Cushing disease or in ectopic ACTH secretion where the source cannot be identified. Mitotane inhibits the
biosynthesis of corticosteroids by blocking the action of 11-β-hydroxylase and cholesterol side chain cleavage enzymes. It also acts by destroying adrenocortical cells that secrete cortisol. Other adrenal enzyme inhibitors, such as aminoglutethimide, metyrapone, trilostane, and ketoconazole, may also be used alone or in combinations to control hypercortisolism. Aminoglutethimide blocks the conversion of cholesterol to pregnenolone in the adrenal cortex, inhibiting the synthesis of cortisol, aldosterone, and androgens. Metyrapone acts by preventing the conversion of 11-deoxycortisol to cortisol. It can also cause hypertension secondary to the accumulation of 11-deoxycorticosterone. Trilostane inhibits the conversion of pregnenolone to progesterone. Ketoconazole is an agent that affects many pathway steps and is excellent in blocking adrenal steroidogenesis.

In ectopic ACTH production, if the source of ACTH secretion can be identified, then the treatment of choice is surgical resection of the tumor. If surgical resection is impossible or if the source of ACTH cannot be identified, then pharmacotherapy is indicated as previously discussed. If the tumor cannot be located, then repeat searches for the tumor should be performed at least yearly. Bilateral adrenalectomy should be performed in the case of failure of pharmacotherapy or failure to locate the tumor after many years.

**GLUCOCORTICOID REPLACEMENT**

After the completion of successful TSS in Cushing disease or excision of an autonomously functioning adrenal adenoma, there will be a period of adrenal insufficiency while the hypothalamic pituitary adrenal axis is recovering. During this period, glucocorticoids should be replaced at the suggested physiologic replacement dose (12–15 mg/m²/day 2 or 3 times daily), as we have recently published. In the immediate postoperative period, stress doses of cortisol should be initiated. These should be weaned relatively rapidly to a physiologic replacement dose; the patient should be followed every few months, and the adrenocortical function should be periodically assessed with a 1-hour ACTH test (normal response is a cortisol level over 18 ug/dL at 30 or 60 minutes after ACTH stimulation).

Patients after unilateral adrenalectomy for a single adrenocortical tumor, require the same replacement and regimen as patients with cushing disease post-TSS. After bilateral adrenalectomy, patients require lifetime replacement with both glucocorticoids (as described previously) and mineralocorticoids (fludrocortisone 0.1–0.3 mg daily). These patients also need stress doses of glucocorticoids immediately postoperatively; they are weaned to physiologic replacement relatively quickly. In addition, stress dosing for acute illness, trauma, or surgical procedures is required for both temporary and permanent adrenal insufficiency.

**PSYCHOSOCIAL IMPLICATIONS**

Cushing syndrome has been associated with multiple psychiatric and psychological disturbances, most commonly emotional lability, depression, and/or anxiety. Other abnormalities have included mania, panic disorder, suicidal ideation, schizophrenia, obsessive–compulsive symptomatology, psychosis, impaired self-esteem, and distorted body image. Significant psychopathology can even remain after remission of hypercortisolism and even after recovery of the HPA axis. Up to 70% of patients will have significant improvements in the psychiatric symptoms gradually after the correction of the hypercortisolism. The author and colleagues recently reported that children with Cushing syndrome may experience a decline in cognitive and school performance 1 year after surgical cure, without any associated psychopathology.
recently reported that active Cushing syndrome, particularly in younger children, was associated with low physical and psychosocial scores, and that despite improvement from before to 1 year after cure, residual impairment remained in physical function and role–emotional impact score. Although most self-reported Cushing syndrome symptoms showed improvement, forgetfulness, unclear thinking, and decreased attention span did not improve after cure.29

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