Chapter 5
Cushing Disease: Diagnosis and Treatment

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Introduction

Endogenous Cushing syndrome (CS) is a rare condition with an estimated incidence of two to five new cases per million people per year; of these, 10% occur in children [1]. Cushing disease (CD) is the most common cause of endogenous hypercortisolemia in older children and adolescents, accounting for more than 75% of all cases [2]. Adrenal disorders are more frequent in infants and younger children, while ectopic corticotropin-releasing hormone (CRH) or adrenocorticotropic hormone (ACTH) production is uncommon in the pediatric population [3–5]. Because of its rarity, CS usually remains unrecognized for a long time resulting in severe consequences, which, if left untreated, may lead to irreversible complications and even death [6]. Careful evaluation of the child suspected to have CS is required to make a prompt and accurate diagnosis of hypercortisolemia and differentiate among the various etiologies, leading to the appropriate management.

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Diagnosis of Cushing Syndrome

The initial evaluation of the patient with suspected hypercortisolemia includes a detailed history and physical examination to identify the characteristic features of CS. Once CS is suspected, the laboratory and imaging evaluation of the patient is directed toward the confirmation of hypercortisolemia and the identification of its source. It is important that no imaging tests (i.e., pituitary magnetic resonance imaging or MRI) are done before the confirmation of the diagnosis of CS because of the high prevalence of incidental findings that may complicate the workup.

History and Physical Examination

Review of history and any medication use is the initial step in the evaluation of the patient. Exposure to glucocorticoid-containing substances (systemic, oral, intranasal, topical, or ocular) should be noted, as the diagnosis of exogenous (iatrogenic) CS is the most common cause of CS [1, 7–9]. Most importantly, the history should include careful observation of the growth chart of the child. A continuous increase of the weight percentile, along with a deceleration of the height percentile, is one of the most important features of CS in children and should prompt further evaluation for hypercortisolemia [10, 11].

Other CS stigmata should be carefully documented in the history and physical examination. Skin manifestations, such as wide purple striae (which, however, are rare in younger children), hirsutism, acne, easy bruising, acanthosis nigricans, and facial plethora, are important and should be assessed in every patient [12, 13]. Additional findings of CS include the presence of myopathy, irregular menses or amenorrhea in pubertal girls, hyperglycemia, hyperlipidemia, and decreased bone mineral density [14–17]. Non-endocrine manifestations include the suppression of the immune system, leading to high risk for infections, and cardiovascular changes with high incidence of hypertension, which might be difficult to manage or result in cerebrovascular ischemic events [18–20]. Furthermore, multiple electrolyte abnormalities are commonly encountered, with more prominent the presence of hypokalemia, hypercalcemia, and hyperglycemia [11, 21].

Laboratory Evaluation

The evaluation of the patient with the suspicion of hypercortisolemia is initially directed to confirming the diagnosis of CS (Fig. 5.1, Table 5.1). According to Endocrine Society guidelines, the initial evaluation of CS should include one or more of the following three tests: [1] measurement of the 24-hour urinary free cortisol (UFC), [2] assessment of the diurnal variation of cortisol secretion by measuring the midnight serum or salivary cortisol level, and [3] low-dose dexamethasone suppression test, typically the 1 mg overnight test.

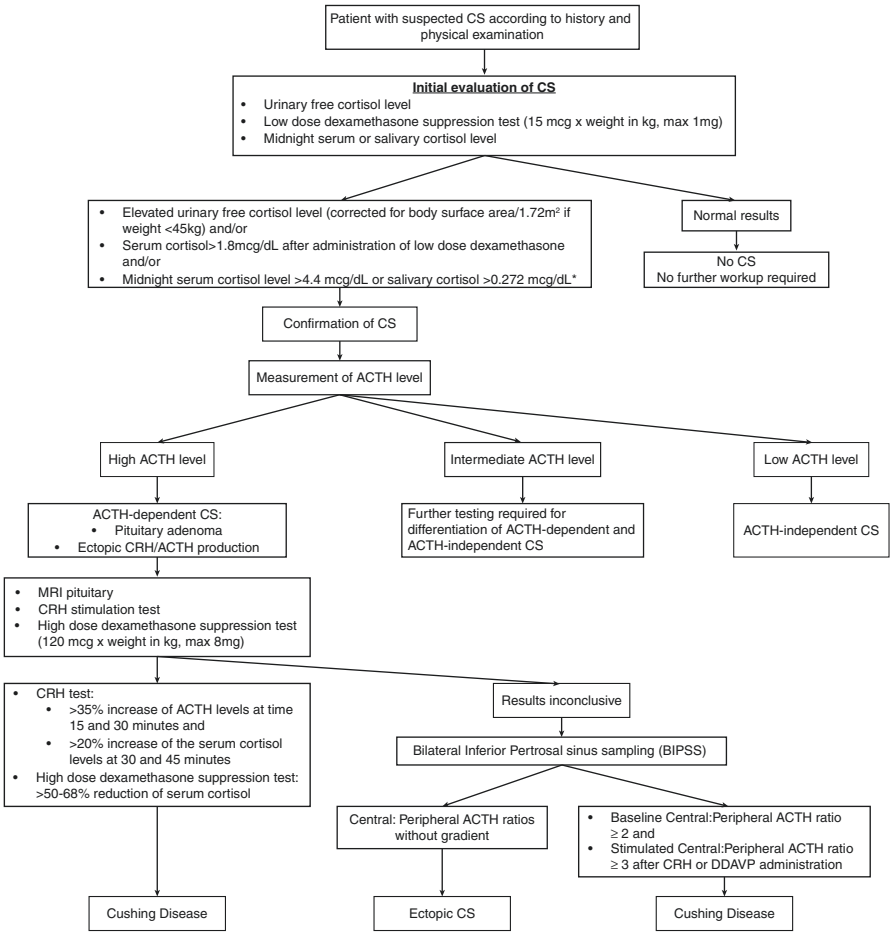

Fig. 5.1 Diagnostic algorithm for the evaluation of CS in children and adolescents
*depends on assay

Table 5.1 Sensitivity and specificity of the various tests used in the diagnostic workup of patients with CS

Test	Sensitivity	Specificity
Elevated UFC	88–89% [41, 42]	90–100% [41, 42]
Midnight serum cortisol >4.4 mcg/dL	99% [41]	100% [41]
Low-dose dexamethasone suppression test (serum cortisol >1.8mcg/dL)	92–100% [58–60]	80% [58–60]
CRH stimulation test (>35% increase of ACTH and >20% increase of cortisol)	74–94% [41, 76, 78]	88–100% [41, 76, 78]
High-dose dexamethasone suppression test (>68% decrease of the serum cortisol)	75–97.5% [41, 78, 84]	88–100% [41, 78, 84]
BIPSS (central/peripheral ACTH ratio ≥2 at baseline and ≥3 after CRH stimulation)	95–98% [11, 86, 88]	97–100% [11, 86, 88]

Assays

It is important that physicians recognize that the assay used for the measurement of hormones can significantly affect the results. Older techniques, like competitive binding assays and antibody-based immunoassays, have lower specificity for cortisol and cross-react with other substrates of similar structure, interfering substances that cannot be removed during the extraction process or exogenous synthetic glucocorticoids, which are sometimes used as part of the diagnostic evaluation in CS [22, 23]. This may result in overestimation of the cortisol concentration.

The advancement of high-performance liquid chromatography/mass spectrometry (LC/MS) has decreased cross-reactivity with these substances and increased the accuracy of the results [24]. At the same time, LC/MS provides the advantage of measuring multiple steroid hormones (including synthetic glucocorticoids) at the same sample [25]. Within the last years, several studies have confirmed the superior performance of LC/MS compared to other conventional assays, especially in conditions where significantly high or low levels are expected, such as CS or adrenal insufficiency [26–28]. The assays have further been validated for the measurement of serum, salivary and urinary, and total or free cortisol levels with high accuracy [29–31].

As expected, assay-specific normal reference ranges and cutoff values should be used, and the results obtained by different assays are not directly comparable [28].

Total and Free Cortisol

Cortisol circulates as more than 95% bound to cortisol binding globulin (CBG) and albumin and less than 5% as free cortisol. Since many of the diagnostic tests used for the evaluation of CS are based on the measurement of total serum cortisol, it is important to emphasize that the final results may be affected by causes that lead to changes of CBG without affecting the active (free) cortisol [32, 33].

Specifically pregnancy and the use of estrogens or oral contraceptive pills (OCPs) increase the hepatic CBG production and lead to elevated total cortisol levels [34–36]. It is therefore recommended that OCPs are discontinued for at least 6 weeks prior to testing [37]. On the other hand, critical illness, low-protein conditions (such as nephrotic syndrome), growth hormone, and insulin result in low CBG and total cortisol levels [38–40].

Urinary Free Cortisol

Measurement of 24-hour UFC is usually the initial screening test for the diagnosis of CS. It yields a high sensitivity (88–89%) and specificity (90–100%), with an estimated accuracy of almost 95% (Table 5.1) [41, 42]. The test, however, requires 24-hour collection of urine for 2 (or ideally 3) consecutive days [41, 42]. This is recommended because urine cortisol excretion may not be consistent in children

with CS, and urine collection might be inadequate the first 24 hours due to inexperience, discomfort, and decreased compliance of the parent and the child. After a 2- or 3-day collection, the average UFC is calculated and corrected for body surface area (BSA) (see below). The urine collection starts after the first morning urine void is discarded. It continues for the remaining day and night and includes the first urine void of the following day. Urine should be preserved in the refrigerator although few hours in room temperature should not affect the results.

During the collection, the child should have a normal fluid intake, avoiding excessive oral fluid consumption and the use or application of any glucocorticoid-containing product [43, 37]. Although exercise has been initially thought to affect the results, this has not been consistently replicated, and thus activity should not be restricted; however, excessive physical and emotional stress may result in false-positive results and should be avoided [44]. Other recommendations that exist in adult patients, such as avoiding smoking and alcohol consumption, rarely apply to children [45, 46]. The interpretation of the UFC results should be corrected for the patient's BSA/1.72m^2 or may follow the adult reference range if the weight of the child is close to that of an adult patient (>45 kg) [37, 47, 48]. Urine creatinine is also measured at the same urine sample, to ensure normal renal function and adequate urine collection [49].

Results that are >four-fold higher than the upper normal limit are considered true positive results [50–52]. However, results that are borderline could be either true positive, potentially representing mild or cyclical CS, or false positive, such as in pseudo-Cushing syndrome that may be seen with anxiety and depression, other concurrent illness, or exposure to alcohol and drugs; additional testing should be pursued, if pseudo-Cushing syndrome is suspected.

UFC has the advantage of being independent of the fluctuations of cortisol levels during the day and CBG concentrations, since only free cortisol is filtered in the urine. It has however several limitations as well. Urine volume may affect the results; healthy adults who were directed to consume higher fluid volumes (5 L of water/day) were found to have higher UFC levels [43]. Urine volume was since found to be an independent factor influencing UFC in children as well, even with the use of LC/MS assays [53–55]. Additionally, abnormal renal function and low glomerular filtration rate (GFR) may lead to falsely decreased levels of UFC, and alternative tests are recommended in these cases [56, 57]. Female gender and lower BMI may also affect measurements, although not all studies have given consistent results [35, 54]. Furthermore, medications can lead to an increase of the UFC level, because of either increased cross-reactivity with the assay (carbamazepine, digoxin, fenofibrate, synthetic glucocorticoids) or inhibition of cortisol metabolism (licorice, carbenoxolone).

Low-Dose Dexamethasone Suppression Test

The low-dose dexamethasone suppression test is based on the physiologic negative feedback of glucocorticoids to the hypothalamus/pituitary level and subsequent suppression of the CRH/ACTH production. In cases of CS, this negative feedback is lost, and autonomous persistent production of cortisol is noted.

The test involves the administration of a low dose of dexamethasone (15mcg/kg, max 1 mg) at 11 pm–12 am and measurement of the serum cortisol level at 8–9 am the following day. Healthy subjects have a suppressed morning cortisol level (<1.8mcg/dL) after dexamethasone administration, while higher results yield a high sensitivity (92–100%) and specificity (80%) for the diagnosis of CS (Table 5.1), although pediatric cutoff values have not been extensively studied [58–60].

The test is easy to perform in the outpatient setting and requires little education for the parent and the child. However, the absorption and metabolism of dexamethasone may be affected by multiple factors, including the consumption of other medications or genetic variations [37, 61]. A concurrent measurement of the dexamethasone level helps to identify these individuals, who may show non-suppressed cortisol levels, without however the presence of CS [62].

Midnight Serum or Salivary Cortisol Measurement

The assessment of the diurnal cortisol variation is based on the well-recognized circadian rhythm of the ACTH and cortisol production: ACTH starts rising overnight and peaks around 6 am–9 am, with a nadir level at 11 pm–2 am, while cortisol peaks between 7:30 am and 8:30 am and then decreases with a nadir value at midnight [63, 64]. Newell-Price et al. studied patients with CS and healthy controls and identified that in all control subjects, the midnight serum cortisol level was <1.8mcg/dL [65]. In CS, the autonomous cortisol production does not follow the circadian rhythm, and thus the loss of the diurnal variation constitutes an important diagnostic tool for the diagnosis of CS.

The collection of the midnight sample requires that the patient is asleep in a quiet environment. The collection of cortisol is performed between 11:30 pm and 12 am; ideally, two samples should be collected (typically, 11:30 pm and 12 midnight), and an average value is calculated. This is why it is best if the test is performed in the inpatient setting where the environmental factors may be closely controlled. In this case, an intravenous catheter has to be placed at least 2 hours prior to the test, and the sample should be drawn without awakening the child. Concurrent measurement of ACTH may also be helpful for further evaluation of the source of hypercortisolemia. In adult patients, various cutoff levels have been suggested for the diagnosis of CS, ranging from 1.8mcg/dL to 7.5mcg/dL [15, 65–68]. A value of 7.5mcg/dL for midnight cortisol is considered a largely confirmatory one for the diagnosis of CS with accuracy over 90%. However, in children this value may be lower: it has been shown that a level of 4.4mcg/dL yields a high sensitivity (99%) and specificity (100%) for the diagnosis of CS (Table 5.1) [41]. If available, the ratio of am/pm cortisol may also be useful for the evaluation of the severity of hypercortisolemia, since it negatively correlates with UFC levels [69].

A night salivary cortisol sample may be used as a substitute of the midnight serum cortisol, because free cortisol diffuses from plasma to saliva, independent of the saliva volume production, and correlates well with the plasma cortisol levels

[70]. The saliva sample may be collected at home by the parent on two consecutive nights while the child sleeps and be maintained in room temperature or in the refrigerator until submitting it to the laboratory. In previous studies in children and adolescents, cutoff levels of 0.272–0.279mcg/dL had a high sensitivity (92.8–100%) and specificity (95.2–100%) for diagnosis of CS, although they should be considered according to the assay used and the current lab reference ranges [71–73].

However, several limitations exist for this study. The circadian rhythm may be altered in some physiologic conditions such as travelling from a country with a different time zone (in which case postponing the testing for at least 1 day for every hour of time difference is recommended) or working on night shifts (rare in children) [2]. Additionally the circadian rhythm is blunted is several pathologic conditions such as depression and critical illness, and thus results should be carefully interpreted. Salivary cortisol measurement may also be affected by substances that inhibit the enzyme 11beta-hydroxysteroid dehydrogenase type 2 (licorice or tobacco) and thus result in falsely elevated levels.

Identification of the Source of Hypercortisolemia

After confirmation of CS, evaluation is directed towards localization of the source of hypercortisolemia and to distinguish ACTH-dependent from ACTH-independent sources; if ACTH dependency is established, it is essential that a pituitary tumor is identified and differentiated from ectopic ACTH-producing lesions (Fig. 5.1). The morning ACTH level is the first test used for the identification of ACTH-dependent CS. The CRH stimulation test and the high-dose dexamethasone suppression test are then helpful in distinguishing a pituitary from an ectopic source of hypercortisolemia. Bilateral inferior petrosal sinus sampling (BIPSS) is considered the gold standard for the final distinction between pituitary ACTH-producing sources and ectopic tumors, but it can only be performed in specialized centers and may not be needed if the pituitary MRI shows unequivocally a tumor. Unfortunately, pituitary MRI can be negative in up to 1/3 of the cases with surgically proven CD (see below).

ACTH Level

A 9 am ACTH level of <30 pg/mL is usually suggestive of an adrenal source, in which case ACTH may be even more suppressed (<5 pg/mL according to some authors); however, in cases of cyclical adrenal CS, ACTH levels may not be suppressed depending on the timing of the test [74]. On the other hand, a morning ACTH level of >30 pg/mL usually indicates an ACTH-dependent source of hypercortisolemia. Intermediate values (10–29 pg/mL) are considered inconclusive and should be interpreted in the context of additional imaging and laboratory tests [74, 75].

It is important to remember that ACTH collection requires preserving the sample in ice and processing as soon as possible, since ACTH is rapidly degraded otherwise, in which cases it will result in falsely low levels [52].

CRH Stimulation Test

The CRH stimulation test involves the administration of CRH (1mcg/kg, max 100mcg) and measurement of the cortisol and ACTH levels at −5, 0, +15, +30, and + 45 minutes afterward. Patients with CD are expected to respond to the CRH administration, with >35% increase of the ACTH peak level (mean value of +15- and +30-minute time points) and >20% increase of the cortisol peak levels (mean value of +30- and +45-minute time points) compared to baseline, although other cutoffs have also been used [76, 77]. The sensitivity of the test is 75–94% with specificity of 88–100% in adults, while in children sensitivity of 74% has been reported (Table 5.1) [41, 76, 78]. Lower sensitivity of the CRH test in children may be due to a higher number of incompletely suppressed hypothalamic-pituitary function in most children with early onset CS.

The CRH stimulation test may be performed at any time of the day, and it usually does not have side effects, although it has been associated with pituitary apoplexy [76, 79, 80]. However it is important to recognize that it does not distinguish patients with CD from normal healthy individuals or patients with pseudo-Cushing syndrome, and thus it should only be performed after the diagnosis of CS has been established, and only in patients with consistent hypercortisolemia that have suppressed hypothalamic-pituitary function [81–83].

High-Dose Dexamethasone Suppression Test

The high-dose dexamethasone test is similar to the low-dose test with the exception of a higher dose of dexamethasone administered (120mcg/kg, max 8 mg). The morning cortisol levels before and after the administration of the dexamethasone are compared, and a >50–68% suppression of the cortisol level is suggestive of CD. The sensitivity is 75–88% in adults with specificity of 86–100%, while in children the accuracy of the test is much higher (sensitivity of 97.5% and specificity of 100%, Table 5.1) [41, 78, 84]. As mentioned above, a dexamethasone level should also be measured to distinguish cases of rapid or slow metabolism of the medication.

Bilateral Inferior Petrosal Sinus Sampling (BIPSS)

Once ACTH-dependent CS has been confirmed (and only then), the gold standard test for the differentiation of CD versus ectopic CS is BIPSS. BIPSS should never be done if the patient is not consistently hypercortisolemic or in cases where ACTH-independent

CS is still possible. The procedure involves catheterization of bilateral petrosal sinuses through the femoral veins [85]. A radiopaque material is infused during the procedure to assure the correct catheterization is performed [86, 87]. Samples for ACTH are collected from each petrosal sinus and from the periphery at baseline, as well as at +3, +5, and +10 minutes after the administration of CRH (1mcg/kg) [86, 87]. A ratio of central/peripheral ACTH of ≥2 at baseline and ≥3 after stimulation with CRH is suggestive of a pituitary adenoma [86]. These cutoffs provide a high sensitivity (95–98%) and specificity (97–100%) for diagnosis of CD in children and adults (Table 5.1) [11, 86, 88].

The test is invasive, and certain complications may occur, such as swelling, erythema or pain at the site of catheterization, headache, or mechanical problems [88, 89]. Brain hemorrhage or other serious complications have also been reported, but, fortunately, they are exceedingly rare in specialized centers. The test is reserved for children with negative MRI and equivocal results on the other diagnostic testing (e.g., a CRH test that suggests CD but a dexamethasone suppression test that points to an ectopic source, especially in the presence of a non-convincing MRI).

The usefulness of BIPSS for lateralization of a pituitary adenoma is less well established; the ratio of ACTH between the two sinuses of ≥1.4 has a sensitivity of only 50–76% [11, 86]. However, in the absence of a visible tumor upon surgery, localization as suggested by BIPSS has been used successfully for the treatment of CD by hemi-hypophysectomy (where half of the gland suggested by the BIPSS to harbor the adenoma is removed).

Imaging Studies

Pituitary adenomas are best demonstrated with high-resolution pituitary MRI with gadolinium contrast administration [90]. Special pituitary protocols with thin slices (1–3 mm) should be requested wherever possible [90]. Specifically spoiled gradient recalled (SPGR) acquisition in the steady state has been shown to have better sensitivity than conventional spin echo (SE) images [91]. Pituitary adenomas appear as hypoenhancing lesions at the pre- and/or the post-contrast images, with differentiation from the hypervascular and hyperenhancing surrounding normal pituitary gland (Fig. 5.2). Specific MRI techniques with thin slices and pituitary protocols are increasing the diagnostic accuracy of the test. Given however the small size of the adenomas in most children, it is not surprising that MRI is positive in only 52–64% of patients with subsequently confirmed CD [11, 91].

Treatment of CD

The first-line treatment for CD is transsphenoidal surgery (TSS) for resection of the pituitary adenoma which may result in cure of the patient. Although there is a high success rate of TSS, up to 20% of patients may experience persistence or recurrence of CS and may require further management. Thus, additional treatment options have been developed, including medical and radiation therapy.

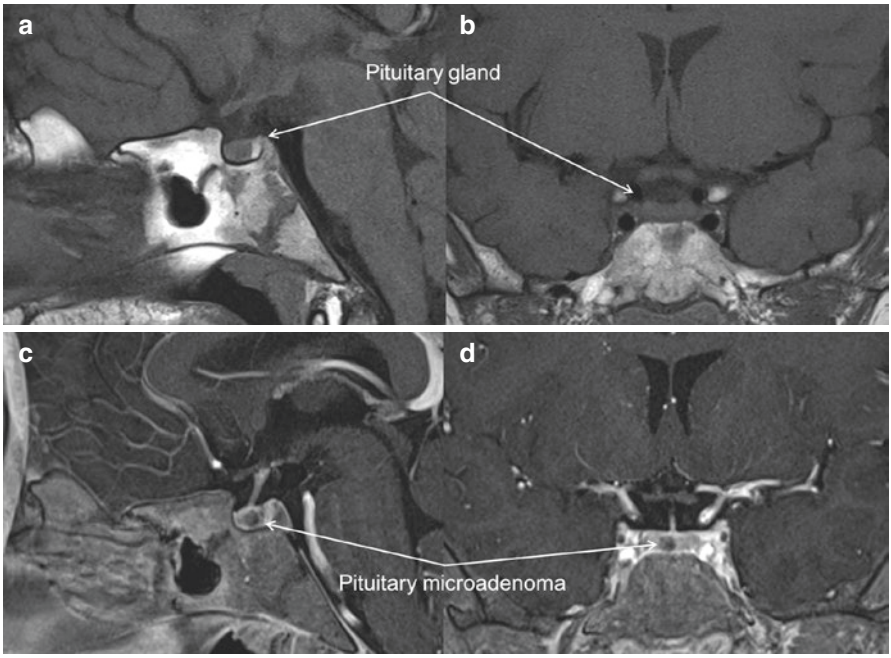

Fig. 5.2 MRI imaging of a 15-year-old patient with CD. The pituitary adenoma is not seen at the pre-contrast sagittal (**a**) or coronal (**b**) T1 images but is present as hypoenhancing lesion at the post-contrast sagittal (**c**) and coronal (**d**) T1 images

Surgical Management

The success rate of TSS depends on the expertise of the center and the surgical team and ranges from 41 to 98% [92]. In a study of a large pediatric cohort in our institution, the immediate remission rate was up to 97% with a recurrence rate of 6% [93]. Details on the current techniques of the transsphenoidal resection of the adenomas will be analyzed elsewhere. In cases where no adenoma is identified, the neurosurgical team may opt to proceed with subtotal or total hypophysectomy. Possible surgical complications of TSS include CSF leak, headaches, infections, deep vein thrombosis, and epistaxis [94–96].

In cases where TSS is unsuccessful and medical management or radiation therapy are not tolerated, contraindicated, or ineffective, or when rapid normalization of hypercortisolemia is required because of comorbidities, bilateral adrenalectomy may be performed [97]. This intervention results in a high percentage of improvement of the clinical findings of CS, with improvement of phenotypic stigmata in 77%, muscular weakness in 93%, hypertension in 80%, and diabetes is 75% of cases [98]. However, it also results in permanent primary adrenal insufficiency with need for lifelong glucocorticoid and mineralocorticoid replacement. Additionally, serial pituitary MRIs are recommended to recognize and treat timely possible increase of a pituitary tumor size, leading to Nelson's syndrome [99].

Postoperative Management

The main goals of the postoperative management of the patients are to identify and treat hormone abnormalities and to assess the success of the surgery in order to predict the risk for recurrence.

The immediate postoperative period of TSS may be complicated by water balance abnormalities in up to 50% of all patients but persists in only a small percentage. The most common abnormality noted is postoperative polyuria (up to 34% of patients), which might be secondary to abnormal antidiuretic hormone (ADH) secretion or excessive fluid administration during the surgery [100]. A biphasic pattern (initial polyuria followed by oliguria and then normalization of the urination pattern) presents in up to 3.4%, whereas the classic triphasic pattern of water imbalance is noted in approximately 1% of patients [100]. In the triphasic pattern, an initial polyuric phase is caused as early as the first postoperative day, due to the acute damage of the pituitary and the stalk, leading to arrest of the secretion of ADH. This is followed by an oliguric phase (post-op day 5–8) due to the syndrome of inappropriate ADH secretion (SIADH) because of degeneration of the terminal axons in the posterior pituitary and then finally by the polyuric phase which may persist chronically [100]. Measurement of urine output and fluid intake, urine specific gravity, serum and urine osmolality, and serum sodium every 6–12 hours after the surgery is usually recommended. The management of diabetes insipidus (DI) involves the use of SC vasopressin (preferred because of the shorter duration of action) or oral desmopressin (nasal sprays may not be used immediately postoperatively in TSS patients for obvious reasons), while SIADH is usually managed with fluid restriction; severe hyponatremia may require hypertonic saline or ADH antagonists [101].

Anterior pituitary hormone deficiencies, transient or permanent, occur in 19–25% of patients after pituitary surgery for CD [11, 102]. Glucocorticoid deficiency is present in patients after a successful resection of a corticotroph adenoma, because of the suppression of the normal corticotroph cells by the adenoma-derived ACTH. Thus, identification of the clinical signs of adrenal insufficiency and replacement with hydrocortisone is vital within the first week after treatment. Delaying the initiation of glucocorticoid treatment until the postoperative testing has been performed, or initiation of dexamethasone instead of hydrocortisone until all the testing is complete, is recommended [103]. The suppression of the hypothalamic-pituitary-adrenal axis reverses within 6–18 months, with a mean time of recovery in children at 12.6 months, with earlier recovery being associated with higher risk for relapse [104, 105].

Additional anterior pituitary hormone deficiencies are also common after TSS for CD. Mild suppression of the thyroid function occurs frequently in children and adolescents before and a few months after TSS. However, they usually remain biochemically euthyroid, and the thyroid suppression resolves within 6 months [106]. Growth hormone suppression during active hypercortisolemia may persist for at least 1 year after resolution of the disease. Treatment with growth hormone could be initiated in cases where the predicted adult height is significantly compromised [107, 108]. Finally, hypogonadism is one of the main findings of active CS, and it may take few months to reverse after treatment.

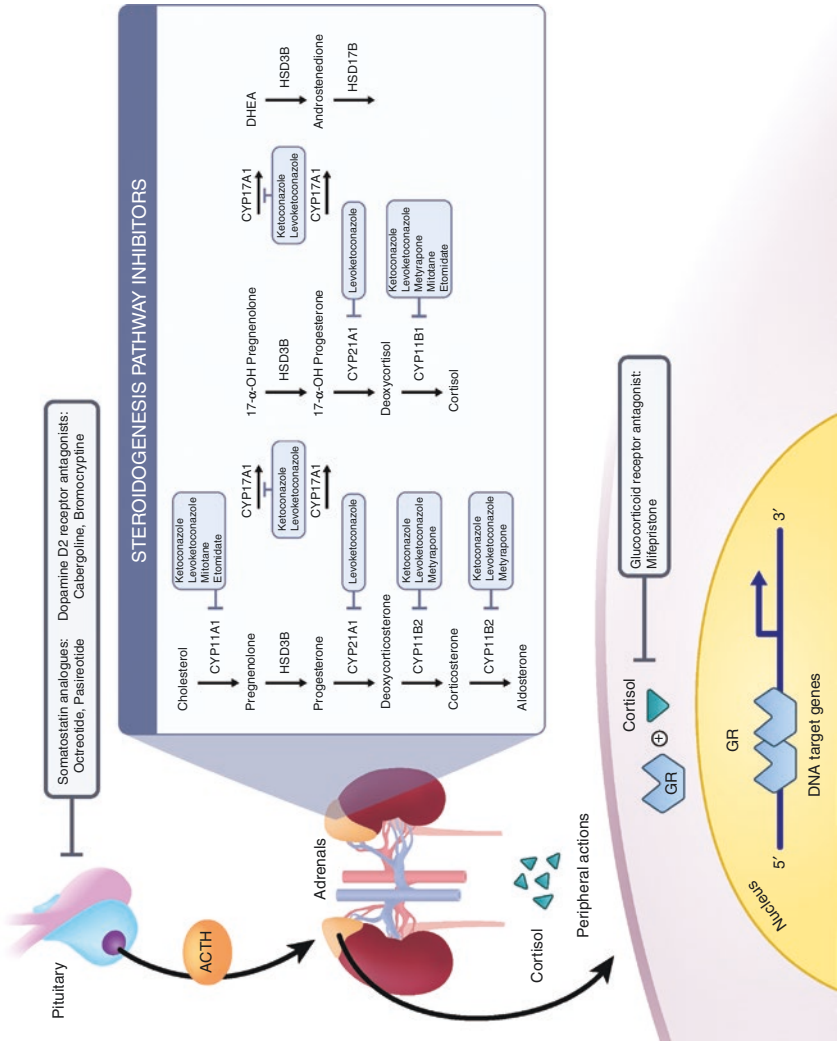

Fig. 5.3 The table shows the various medical therapies for persistent or recurrent CS and their target organs

The postoperative testing, aiming at the identification of residual disease or remission, includes the morning plasma ACTH and cortisol levels and the postoperative CRH test, while the 24-hour UFC is of limited value [93]. We usually measure morning (8 am) plasma cortisol and ACTH levels for the first postoperative week. In adults various cutoff values for the cortisol level (<1.8–5mcg/dL) are being used, and it is suggested that persistent postoperative morning cortisol of <2mcg/dL is associated with a low relapse rate (<10%) [93, 103, 109–111]. In children specifically, a single level of 8 am cortisol nadir <4.7mcg/dL is the most accurate cutoff value to differentiate remission from recurrence, with sensitivity of 50% and specificity of 100%, while mean cortisol level of <6.5mcg/dL provided a sensitivity of 50% with 100% specificity for identification of remission. Additionally, an 8 am nadir ACTH level of <10.8 pg/mL is the best cutoff value for differentiation of remission and risk for relapse, with sensitivity of 75% and specificity of 97% [93].

The postoperative CRH test is similar (but not identical) to the CRH test performed during the initial workup of the patient, and it is usually performed on postoperative days 9–10. A dose of CRH of 1mcg/kg, max 100mcg is administered, and samples for cortisol and ACTH are drawn at −15, 0, +5, +15, +30, +60, +90, and +120 minutes after the administration [112]. A normal response to the CRH indicates higher recurrence rate, and, specifically in children, a peak ACTH level of >32 pg/mL (sensitivity 100%, specificity 92%) and a peak cortisol level of >10 mcg/dL (sensitivity 100%, specificity 88%) provide the most accurate cutoff levels for the prediction of recurrence [93].

Medical Management

In patients who failed TSS or CS relapsed, medical therapy with or without radiation are alternative options in order to control hypercortisolemia. The main categories of medications used in CD include inhibitors of the steroidogenesis, pituitary-directed therapies, and antagonists of the cortisol action in the peripheral tissues. Several newer agents are under investigation in order to provide more efficient suppression of the cortisol production with fewer side effects (Fig. 5.3). These are discussed in more detail below.

Inhibitors of Steroidogenesis

Ketoconazole

Ketoconazole is an imidazole derivative that has been primarily used for its antifungal properties [113]. However, it has been recognized that ketoconazole (and importantly other imidazole derivatives) also inhibits P450 enzymes involved in steroidogenesis and specifically cholesterol side-chain cleavage enzyme (*CYP11A1*),

17,20 lyase and hydroxylase (*CYP17A1*), 11beta-hydroxylase (*CYP11B1*), and 18-hydroxylase (*CYP11B2*), resulting in suppression of the adrenal hormone production [114, 115]. The dose of ketoconazole required for adrenal suppression in CS is higher than the recommended for antifungal use and ranges from 200 to 1200 mg/day [116]. In a large retrospective study by Castinetti et al. including 200 patients with CS, complete or partial control of hypercortisolemia was achieved in up to 76%, with complete response in up to 50% at a mean dose of 780 mg/day. Previous smaller studies have shown response rates at 25–100%, with concurrent significant control of the CS complications, such as diabetes, hypertension, and hypokalemia [116–121].

The major side effect of ketoconazole is the risk for hepatic toxicity and liver failure, which is demonstrated as a "black box" warning by the FDA [122, 123]. Elevation of the liver enzymes is noted in up to 16% of patients, while significant increase (>five-fold the upper limit) is much more rare (3%) [116]. In most cases the liver enzyme elevation resolves 2–4 weeks after discontinuation or decrease of the dose of ketoconazole [116]. Measurement of the liver enzymes once weekly for the first month of treatment is recommended. If the liver enzymes are increased <five-fold, then decrease of the dose by 200 mg/day could be done with close follow-up, while discontinuation of the treatment is recommended if the liver enzymes increase for >five-fold [116]. Additional side effects include iatrogenic adrenal insufficiency (usually managed with replacement of glucocorticoids), GI complains, pruritic rash, fatigue, hypogonadism, gynecomastia, hair loss, leg edema, and muscle pain [116]. Levoketoconazole, an enantiomer of ketoconazole, is a more potent inhibitor with possibly lower side effects which is currently under investigation for management of CS [124].

Metyrapone

Another steroidogenesis inhibitor used for the management of hypercortisolemia is metyrapone, which inhibits the enzymes 11beta-hydroxylase (*CYP11B1*) and 18-hydroxylase (*CYP11B2*) [125]. In patients with CS treated with metyrapone, response was noted in up to 50–75%, in doses of 500–6000 mg/day [126–128].

Possible side effects present in up to 25% of the patients, with GI upset being the most common, followed by adrenal insufficiency, hirsutism (in women) and acne (because of the accumulation of adrenal androgens), edema, hypertension, and hypoglycemia [126, 128].

Mitotane

Mitotane is a derivative of the insecticide dichlorodiphenyltrichloroethane, and it is commonly used as adjuvant therapy in the management of adrenocortical carcinoma [129, 130]. Because of its steroidogenesis inhibitory properties on *CYP11A1* and *CYP11B1* and the suppression of cell growth, it has also been used in patients

with persistent CS as monotherapy or in combination with other medications [131–135]. The complete response rate is 70–80%, while most of the patients achieve some decrease of their UFC levels. The mean required dose is 2.5 g/day, lower than the recommended for treatment of adrenocortical carcinoma [133, 134].

However, mitotane is accompanied by serious toxicity, and it requires frequent monitoring of its plasma levels. Major side effects include GI complaints, hepatic toxicity, neurologic problems, hyperlipidemia, neutropenia, hypogonadism, and gynecomastia [130, 134]. Additionally, because of its lipophilic properties, it has a delayed onset of action, leading to a mean time to response of 4–16 months [133, 134]. Of note the phenomenon of "emergent pituitary adenoma," where a pituitary adenoma becomes evident in MRI after medical treatment, has been described in 25% of patients treated with mitotane, possibly related to the lack of the cortisol feedback to the pituitary level, and thus led to successful TSS and immediate remission [134].

Glucocorticoid Receptor Antagonists

Mifepristone

A more targeted therapeutic option is aiming toward the glucocorticoid receptor (GR) in the periphery. Mifepristone is currently FDA approved for the management of adults with CS and associated diabetes or glucose intolerance who failed surgical management [136]. Mifepristone is a glucocorticoid and progesterone receptor antagonist, which has a much higher affinity for the GR than cortisol [137]. Although its use increases the serum ACTH and cortisol levels, it also improves several symptoms of hypercortisolemia, including weight, hypertension, and hyperglycemia in >50, 38, and 60% of patients, respectively, while the overall clinical response was 87% in a large prospective study (SEISMIC study) [138–140].

Major side effects include GI complaints, fatigue, edema, headaches, dizziness, musculoskeletal complaints, infections, hypokalemia, clinical adrenal insufficiency (not associated with the biochemical values), and endometrial hypertrophy [140–142]. Mifepristone is contraindicated in pregnancy and endometrial hyperplasia, while care should be taken in cases of renal insufficiency.

Pituitary-Directed Medications

Somatostatin Analogues

Corticotroph adenomas express somatostatin receptors (SSTRs), and somatostatin analogues have been used for their management. The molecules that were initially developed, such as octreotide, seem to have preferential binding to SSTR-2, and their efficacy on corticotropinomas has been low [143–145]. However newer

analogues, such as pasireotide, which exhibit more potent binding of the SSTRs and specifically SSTR-5 which is the most important in corticotroph cells, have been more promising [146, 147]. Specifically in a phase III clinical trial of pasireotide including 162 adult patients with CD (mean age of 40 years old) over 12 months, pasireotide use resulted in complete control of the UFC in up to 26% of the patients at the 6-month time point, while an additional 18% of the patients showed partial control [148]. This control seemed to be persistent at their long-term follow-up [149, 150]. Pasireotide is currently FDA approved for treatment of adult patients with CD who failed or are not eligible for surgical management [151].

Potential side effects result from the suppression of the secretion of other hormones, since somatostatin normally regulates various hormone secretion [152]. The most common side effect is diarrhea, nausea, abdominal pain, and headaches. Furthermore, the cholecystokinin secretion is reduced leading to gallbladder disorders (sludge and gallstones) [148, 153]. Hyperglycemia is a major side effect, because of the suppression of the insulin secretion, which is dose dependent and might be attenuated after repeat use of the medication [148, 153]. Concomitant therapy with antihyperglycemic agents has been tried and shown to partially reverse this effect [154]. Additionally, cardiovascular effects and elevation of the liver enzymes have also been noted [148]. Most of the side effects can be treated with temporary reduction of the medication dose [153, 155].

Dopamine D2 Receptor Agonists

Dopamine D2 receptor agonists, such as cabergoline and bromocriptine, have been used for CD given the identification of dopamine receptors in corticotroph adenoma cells [156, 157]. Their success rate however is not very high. Bromocriptine has shown lower efficacy rates than cabergoline, possibly related to the higher affinity of the dopamine receptor and longer duration of action of the latter [158].

The response rate of cabergoline has been ranging from 20 to 50% in several studies, at a mean dose of 2.1–6 mg/week [159–161]. Although there are limited serious side effects reported, the possibility of treatment escape, which occurs in up to 39% of initial responders, or treatment intolerance decreases the long-term success rate to approximately 23% despite the necessary dose adjustments [161]. No specific factor has been shown to predict the response of an individual to the cabergoline treatment. In patients who have incomplete response to other agents, addition of a dopamine agonist could be considered as an adjunctive therapy [161].

Other Pharmaceutical Options

Etomidate is an imidazole agent which is widely used for sedation as an intravenous drug. It inhibits the 11beta-hydroxylase (*CYP11B1*) and the side chain cleavage (*CYP11A1*) enzymes, leading to reduced cortisol production. Although case reports

of its use in the management of CS have been reported, it is not widely used in this population due to its requirement for intravenous administration, side effects, and the availability of alternative medications. Because of its rapid onset of action, it can be used in acutely ill patients when immediate resolution of CS is sought. Then patients may be switched to oral therapy with other agents.

Newer 11beta hydroxylase inhibitors, melanocortin-2 receptor (MC2-R) antagonists, combined somatostatin and dopamine receptor antagonists, PPAR-gamma receptor agonists, EGFR inhibitors, and others, are under investigation, but limited data are currently available for their efficacy in CS [162].

Radiation Therapy

Conventional and most recently stereotactic and proton beam radiation therapy is an alternative option for patients who fail the surgical management for CD or relapse. Conventional radiation therapy leads to successful biochemical control in 46–100% of patients [163, 164]. Stereotactic radiation, directed more precisely to the adenoma, has a reported biochemical remission rate of 59–100%, while proton therapy resulted in complete response in up to 67% of patients [165, 166]. The mean time to biochemical control of hypercortisolemia is long, although it might be shorter in the pediatric population, around 1 year post-therapy [167].

The most common side effect of radiation therapy is hypopituitarism which presents in 10–52% of the adult patients receiving conventional therapy, 24–36% of patients after stereotactic therapy, and in up to 57% after proton therapy [164–166, 168]. In a study specifically in children with CD who received conventional radiation therapy, it was noted that aside from growth hormone deficiency which was identified in all patients, gonadotropin or thyroid deficiency has not developed in the seven patients who were followed up to 12 years [167]. Other complications include the development of secondary intracranial tumors, radiation-induced necrosis of brain tissue, leukoencephalopathy, and optic chiasm involvement with visual complications, but these are more rare [164, 169, 170].

Conclusion

Pituitary corticotroph adenomas are the most common cause of endogenous CS in children. The diagnosis of CS involves various tests, in order to establish the correct diagnosis. The localization of the source of hypercortisolemia is very important prior to any intervention. When CD is confirmed, TSS is the first-line therapy. For patients who fail the surgical treatment or relapse, several medical options exist, while radiation therapy is often used in combination to achieve biochemical and clinical remission of the hypercortisolemia. Newer agents are currently investigated for more precise and effective outcomes.

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