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Cushing's disease

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Abstract Cushing's disease, i.e., pituitary ACTH-secreting adenoma causing excess glucocorticoid secretion, is a rare disease with significant mortality and morbidity. Timely diagnosis and appropriate treatment can alter the course of the disease and are therefore mandatory. First step of the diagnostic work-up is the endogenous glucocorticoid excess by measurement of urinary free cortisol, cortisol circadian rhythmicity or suppression by low doses of dexamethasone. In patients with equivocal results, second line tests, such as the dexamethasone-suppressed CRH test and desmopressin stimulation, usually enable the diagnosis to be confirmed. Measurement of plasma ACTH then allows the distinction between ACTH-dependent (e.g., pituitary or extrapituitary neuroendocrine tumors) and ACTH-independent causes (e.g., adrenal tumors). The last step in the diagnostic algorhythm is often the most fraught with problems as the distinction between Cushing's disease and ectopic ACTH secretion relies on judicious interpretation of several diagnostic procedures. Positive responses to stimulation with CRH and inhibition by high doses of dexamethasone, if concurrent, enable a pituitary origin to be established whereas conflicting results call for inferior petrosal sinus sampling, the latter to be performed in experienced centres only. Visualisation of the tumor at pituitary imaging is helpful but not required for the diagnosis, as microadenomas often remain undectected by MRI and/or CT scan and, on the other hand, visualisation of a non-secreting incidentaloma may be misleading. Surgical removal of the pituitary tumor is the optimal treatment choice and should be attempted in every patient. Surgical failures as well as relapses can be treated by radiotherapy, medical therapy or, if necessary, bilateral adrenalectomy. Finally, patients cured of Cushing's disease require long-term monitoring given the risk of relapse and clinical burden of associated ailments.

Keywords Cushing's disease · ACTH-secreting pituitary adenoma · CRH stimulation · Inferior petrosal sinus sampling

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Demographic and clinical findings

Cushing's disease defines the clinical picture of an ACTH-secreting pituitary tumor, almost exclusively a benign adenoma, leading to overproduction of glucocorticoid steroids by the adrenal cortex and clinical features of glucocorticoid excess. Excess corticosteroid secretion may also be due to production of ACTH or its releasing factor, CRH, by an extrapituitary neuroendocrine tumor (i.e., ectopic ACTH/CRH secretion) or to primary adrenal lesions (e.g., adenoma, carcinoma, hyperplasia and dysplasia) as well as to steroid therapy. All causes of inappropriately high cortisol secretion are grouped in the term "Cushing's syndrome" with pituitary tumors making up the lion's share (over 70% of all cases of Cushing's syndrome). Irrespective of the underlying etiology, glucocorticoid excess is characterized by a disruption of cortisol circadian rhythmicity and altered feedback mechanisms.

Cushing's disease is an uncommon disorder with an estimated incidence of 2.4 new cases per million inhabitants per year [1] occurring mostly in young adult females (mean age at diagnosis is 36 years). Both sexes are equally affected in prepubertal Cushing's disease [2]. The ACTH-secreting pituitary adenoma is sporadic except for rare cases in patients with familial multiple endocrine neoplasia type 1 [3].

Clinical features of hypercortisolism include weight gain and truncal obesity with supraclavicular and cervical fat depots ("buffalo hump"), rounded "moon-like" facies, thinned skin with purple striae and multiple ecchymoses, acne and hirsutism, and proximal muscle weakness caused by muscle atrophy. Hypertension, osteopenia, menstrual irregularities and neuropsychological disturbances (e.g., depression, irritability, sleep disturbance, cognitive defects or even frank psychosis) further characterize patients with Cushing's disease. Clinical chemistry may reveal glucose intolerance or frank diabetes, hypokalemia and leukocytosis. Cause of death in patients with untreated Cushing's disease are systemic fungal infections, most often due to opportunistic agents such as aspergillus fumigatus [4], or cardiovascular events, such as coronary artery disease and congestive heart failure. Overall mortality of patients with unremitted hypercortisolism is 4–5 greater than the general population [5] thus justifying exhaustive testing procedures for a timely diagnosis.

Diagnosis

Biochemical diagnosis

The diagnosis of Cushing's disease requires a series of first line tests, namely measurement of *24 hour urinary free cortisol secretion* (UFC) and the evaluation of *cortisol circadian rhythmicity* and *suppressibility by low-dose dexamethasone*. Cortisol secretion fluctuates from day to day thus at least three 24 h urine collections are expedient to properly apprise endogenous cortisol secretion. *UFC measurement* may be performed by radioimmunoassay or immunometric assays, or as recently proposed, high performance liquid chromatography (HPLC) or even mass spectrometry gas chromatography (MSGC). Immunoassays are well validated and can reliably detect Cushing's syndrome (over 96% sensitivity according to Perry and Grossman) [6] whereas HPLC and MSGC may offer greater diagnostic accuracy but are expensive and require large-scale validation. It is worth recalling that a markedly reduced glomerular filtration rate (<30 ml/min) invalidates UFC measurements [7] and that several compounds, both endogenous and exogenous, e.g. cortisol metabolites, phenofibrate, may interfere with UFC measurement. Correction of UFC by body surface area is necessary for children: normal values are <70 μg (193 nmol)/m^2/day [8]. Markedly elevated UFC levels are clearly diagnostic of Cushing's syndrome while mildly supranormal values may also be due to pseudoCushing states, i.e., conditions mimicking Cushing's syndrome. PseudoCushing may stem from depression, alcoholism, obesity and polycystic ovary syndrome, and further testing is required to distinguish between these two entities. The possibility of cyclical Cushing's disease, characterized by spells of hypercortisolism alternated with normal UFC secretion, should also be considered. Measurement of cortisol at midnight enables the evaluation of *circadian rhythmicity*. Diagnostic criteria vary somewhat and several cut-offs are being used. The diagnosis of Cushing's disease is next to assured with midnight serum cortisol levels greater than 7.5 μg/dl (207 nmol/l) [9] and refuted by levels below 5 μg/dl (140 nmol/l) or even 1.8 μg/dl (50 nmol/l) [10, 11]. Intermediate results require confirmation by second-line testing (see later). Salivary midnight cortisol appears to be a convenient alternative to serum sampling [12] although further large-scale studies are required. Suppression with small doses of dexamethasone can be performed with 1 overnight or 2 mg daily for two days in adults whereas the dosage for children is not well defined (10–40 μg/kg body weight, max. 1 mg at midnight or 2 mg for two days) [13–15]. *Nugent's overnight suppression test* requires the measurement of morning serum cortisol following 1 mg of dexamethasone administration at 11 pm the previous evening. Sensitivity for the detection of Cushing's syndrome ranges from 95 to 100% with cortisol levels below 1.8 μg/dl (50 nmol/l) or 5 μg/dl (140 nmol/l) [16, 17]. In alternative, 0.5 mg dexamethasone can be administered every 6 h for two days (*Liddle's low dose dexamethasone suppression test, LDDST*), and UFC or 17 hydroxycorticosteroids (17OHCS) or serum cortisol measured after 48 h. UFC levels below 20 μg/24 h (55 nmol/24 h) or 17OHCS below 3.5 mg/24 h (7 μmol/24 h) on the second day of dexamethasone administration exclude Cushing's syndrome. Either 1.4 μg/dl (38 nmol/l) or 1.8 μg/dl (50 nmol/l) are accepted cut-offs for serum cortisol [18] ensuring 98% sensitivity for Cushing's syndrome. The diagnostic accuracy of dexamethasone suppression tests may be undermined by impaired drug absorption or concomitant use of drugs that accelerate dexamethasone metabolism by the liver, e.g. phenytoin, or of estrogen or tamoxiphen that enhance corticosteroid binding globulin (CBG) production.

In patients with discordant test responses, second-line testing may be performed in order to distinguish between mild Cushing's syndrome and pseudoCushing states. Out of several tests proposed to this purpose, the *dexamethasone-suppressed CRH test* and *desmopressin stimulation* appear the most useful, although no large series has yet been reported with either test. Cortisol levels greater than 1.4 μg/dl (38 nmol/l) within 15 min of CRH administration (100 μg iv) after 2 mg dexamethasone for 2 days confirm the diagnosis of Cushing's syndrome [19] and the same holds true if the ACTH increase after 10 μg desmopressin administration exceeds 50% of baseline or 27 pg/ml (6 pmol/l) [20, 21].

Once Cushing's syndrome has been diagnosed, etiological diagnosis work-up is required beginning with the measurement of plasma ACTH concentrations in order to establish ACTH-dependency and exclude primary adrenal

causes. In patients with Cushing's disease, *ACTH values* range from low-normal concentrations, e.g. 10–20 pg/ml (2.2–4.4 pmol/l), to clearly elevated levels (over 200 pg/ml; 44 pmol/l). However, results of plasma ACTH measurement should be judged with caution since they may appear measurable or even normal in cases of ACTH-independent Cushing's syndrome. The pituitary origin of hypercortisolism can be confirmed by assessing the response to *CRH stimulation* given the fact that patients with adrenal Cushing's syndrome and unsuppressed ACTH levels as well as patients with ACTH-secreting extrapituitary neuroendocrine tumors fail to respond to the hypothalamic releasing factor. Pronounced responsivity to CRH, indeed, is the hallmark of ACTH-secreting pituitary tumors [22]. Commonly accepted response criteria are a 35–50% ACTH increase over baseline and/or 20–50% cortisol increment over baseline, respectively, within 15–30 min and within 30–45 min of 1 μg/kg or 100 μg ovine CRH injection. Sensitivity of the ACTH response is about 85% [16, 22] whereas somewhat lower yields have been recorded using the cortisol response (sensitivity from 59 to 91%) [16, 23]. Specificity, i.e. the correct identification of extrapituitary ACTH-secreting tumors, for the ACTH response ranges between 95% [22] and 100% [16, 23] although these tumors may occasionally respond to CRH [24]. The *high dose dexamethasone suppression test* (*HDDST*) also allows the distinction of pituitary and extrapituitary ACTH-secreting tumors, albeit with a lower diagnostic efficacy, as neuroendocrine tumors are mostly insensitive to cortisol feedback mechanisms whereas pituitary tumors exhibit a resetting of feedback at a higher set point. Administration of 8 mg dexamethasone overnight or 8 mg daily (2 mg every 6 h) for two days is followed by measurement of serum cortisol at 24 and 48 h and/or urinary cortisol or 17 OHCS on the second day. In children, the dosage is 120–160 μg/kg/daily (max. 2 mg every 6 h) that should be administered for two days q.i.d. [13, 15]. Suppression of serum cortisol by at least 60% of baseline assures 85% sensitivity and 90% specificity for Cushing's disease [25]; steeper cut-offs (e.g., 80% of baseline) achieve better specificity at the expense of sensitivity [16, 26]. The same was observed for UFC and 17OHCS measured on the second day of dexamethasone administration with 90% and 69% suppression, respectively, yielding approximately 80% sensitivity [27]. Performing both tests increases the risk of discordant responses [28], but strengthens the diagnosis of Cushing's disease if both tests concur. Indeed, the likelihood of ectopic ACTH secretion is next to nonexistent if a positive response to both tests is recorded [25].

Pituitary imaging

Pituitary imaging with enhancement visualises the pituitary tumor in some 60% of patients with Cushing's disease, the remaining microadenomas being too small for detection by either MR or CT [16]. Macroadenomas, i.e., tumors larger than 1 cm in diameter, occur in a scant 20% of patients [16] while small incidental tumors may be observed also in patients with ectopic ACTH secretion; thus, small pituitary lesions (<5 mm) should be viewed in context with dynamic testing. Conversely, lesions greater than 6 mm in patients with CRH and HDDST testing indicative of a pituitary tumor substantiate the diagnosis of Cushing's disease and the patient can be sent to the neurosurgeon forthwith.

Central venous sampling

If dynamic testing or pituitary imaging did not yield conclusive etiologic evidence, *bilateral inferior petrosal sinus sampling (BIPSS)* should be performed in order to establish the presence or absence of a center-periphery ACTH gradient. Plasma ACTH concentrations are measured in both petrosal sinuses before and 3–15 min after CRH administration and values measured at these sites are compared with levels measured from simultaneous brachial vein sampling. Angiography is essential to attest to correct positioning of catheters and drainage pattern as hypoplastic or plexiform inferior petrosal sinus may interfere with test accuracy. Baseline and CRH-stimulated center-periphery ACTH gradients greater than 2 and 3, respectively, yield 85–97% sensitivity for Cushing's disease [16, 29]. Specificity is near to absolute [30] as significant post CRH gradients have been reported only in the exceptional patient with ectopic ACTH secretion [31]. Conversely, it should be recalled that an absent gradient does not exclude Cushing's disease, as false negatives are increasingly being reported; by virtue of its greater prevalence, Cushing's disease is still more likely than ectopic ACTH secretion in patients with absent center-periphery gradient [32]. Prediction of the site of the pituitary tumor by BIPSS is less reliable, with over one-third of predictions not confirmed by surgery [16]. The need for specific expertise and the risk of thromboembolic events restrict this procedure to highly specialized centers. *Jugular venous sampling* and *cavernous sinus sampling* have been proposed in alternative to BIPSS but do not appear to offer clear advantages [33, 34].

Complications

Cardiovascular risk

Patients with active Cushing's disease present an increased incidence of cardiovascular events, such as coronary artery disease, congestive heart failure and cardiac infarction, which contribute to a four-fold higher mortality rate compared to an age- and sex-matched population [35]. This

increased cardiovascular risk is closely related with features of the metabolic syndrome, e.g., hypertension, obesity, diabetes, hyperlipidemia and hypercoagulability [36].

Hypertension is present in 75–85% of adult patients and over half of children with Cushing's disease and warrants both prompt treatment and in depth evaluation of target organ damage. Commonly used antihypertensive agents, e.g., thiazides, angiotensin-converting enzyme inhibitors, calcium antagonists and spironolactone if hypokalemia is present, are usually capable of containing diurnal and nocturnal blood pressure elevations. Echocardiography, exercise ECG and echo-Doppler sonography are needed to assess carotid and cardiac morphology and function [37]. *Abdominal obesity* is a known cardiovascular risk factor *per se* [38] and is ascertained by measurement of waist circumference (WC) or by waist-to-hip ratio (WHR). WC >102 cm (>40 inches) in men and >88 cm (>35 inches) in women are associated with a 24% relative risk for cardiovascular disease death [36]. *Glucose intolerance* and *frank diabetes* affect 20 to 60% of patients with Cushing's disease and require diet, oral antihyperglycemic agents or insulin administration. Fasting or post-glucose load glycemia should be routinely measured in these patients. Insulin resistance is almost invariably present and can easily be assessed by HOMA-IR or Quicki index. More complex procedures, such as euglycemic hyperinsulinemic clamp, are not warranted. Excess glucocorticoid secretion leads to *dyslipidemia* with increased FFA, VLDL and LDL levels, hypertriglyceridemia and hypercholesterolemia, whereas HDL levels are mostly unaffected [39]. Thiazolinidinediones may be of particular interest in these patients, given combined effect on insulin sensitivity and adipocyte proliferation and differentiation and -possibly- on the tumoral pituitary corticotrope itself [40]. Lastly, alterations in coagulation and fibrinolysis [41] give rise to a *prothrombotic state*, in turn responsible for 4-fold increased risk of pulmonary embolism and deep vein thrombosis [42]. Heparinization prior to surgery or BIPSS has been recommended by some authors [43].

Osteoporosis and alterations in calcium metabolism

Pathologic rib and vertebral fractures affect 30–50% of patients with Cushing's disease. In addition, aseptic necrosis of the femoral or humeral head may occur. Given these occurrences, vertebral dual energy X-ray absorptiometry (DEXA) and chest Rx have to be performed to detect osteopenia or inapparent fractures. Osteoporosis may also affect children with Cushing's disease and impair the attainment of peak bone mass [44]. Treatment of osteoporosis should be started as soon as possible, even in patients with active disease, as normalization of bone mass is difficult to achieve [45]. Calcium and Vitamin D supplementation should be used in association with thiazide diuretics in order to reduce calcium excretion, given the increased risk of nephrolithiasis in Cushing's disease [46]. If bone loss is severe, treatment with biphosphonates should be attempted [47]. It should also be recalled that hypercalcemia may occur in these patients.

Concomitant correction of other endocrine deficiencies (e.g., hypogonadism) may be necessary to potentiate the recovery of bone mass, but correction of hypercortisolism remains paramount.

Psychiatric disturbances

Psychological alterations, ranging from irritability and emotional liability to severe depression, suicidal behaviour and manic episodes, affect up to 80% of patients with Cushing's disease. Cognition is often impaired in adult patients while an intense preoccupation with learning leads hypercortisolemic children to excel at school [48]. If necessary, antidepressant agents (e.g., tricyclics or selective serotonin reuptake inhibitors) may be helpful [49]. Psychological liability or underlying psychiatric disorders often persist after cure of hypercortisolism but benefit from appropriate drug treatment.

Endocrine changes

Growth hormone (GH) as well as gonadal function is notably impaired in patients with Cushing's disease, a consequence of hypercortisolism or direct pituitary-hypothalamic interactions. GH deficiency [50] is particularly relevant in children as it may contribute to the stunted growth. Investigation of the GH-IGF-1 axis is warranted in all patients especially after cure, in view of the possible persistence of deficient GH secretion. Hypogonadism may worsen bone and muscle loss but estrogen replacement therapy during the active phase is contraindicated given the prothrombotic state. Mild secondary hypothyroidism and thyroid nodules are often encountered in patients with Cushing's disease [51] and can be managed expectantly.

Ocular complaints

Up to one-third of patients with Cushing's disease present ocular hypertension and exophthalmos while more severe diseases, such as chorioretinopathy, fundus anomalies and visual field defects, are rare [52]. Ophthalmic evaluation is mandatory, especially in patients with pituitary macroadenomas.

Treatment

Treatment of Cushing's disease has to be initiated as soon as possible in order to avoid progression of the

above-mentioned complications. The aim of treatment is removal of the tumor and normalization of ACTH and cortisol secretion while preserving pituitary function. Removal or destruction of the pituitary tumor achieves a causal correction of hypercortisolism while adrenal-directed approaches, both surgical and medical, contain excess cortisol secretion but do not cure Cushing's disease *per se*.

Pituitary surgery

Transsphenoidal pituitary surgery is the most rational treatment for pituitary ACTH-secreting adenoma. Surgical mortality is next to nonexistent (<1%) and morbidity acceptably low (6–15%) [53], with transient diabetes insipidus and liquorrhea as the most frequent perisurgical complaints. Adenomectomy (i.e., pituitary-sparing selective removal of the tumor) is preferred to blind hemihypophysectomy or wedge resection. Success rate varies from 60 to 80% depending on size and location of the tumor, with macroadenomas and locally invasive tumors achieving a less favourable outcome, i.e., less than 50% [54] and, of utmost importance, experience of the neurosurgeon. Identification of the ACTH-secreting tumor at pathological analysis is a good prognostic indicator for cure [55]. Repeat pituitary surgery has been performed in surgical failures [56, 57] or tumoral regrowth with lesser success [16] and greater risk of permanent hypopituitarism and diabetes insipidus than first surgery. Generous steroid replacement therapy (200–300 mg hydrocortisone) should be administered intra- and postoperatively, followed by progressive tapering to maintenance dosage (hydrocortisone 30 mg/d or prednisone 7.5 mg/d or cortisone acetate 37.5 mg/d). Treatment should be continued until inhibition of the HPA axis resolves. Criteria to establish cure of Cushing's disease are discussed below.

Pituitary radiation

Although ACTH-secreting pituitary tumors are less sensitive to radiation compared with other pituitary tumors, pituitary radiation remains a rational and reasonable choice, possibly offering even better outcomes than surgery in children [58]. Radiation therapy is currently performed by most centers after failure of pituitary surgery or in inoperable patients, e.g., tumor extension into the cavernous sinus or above the sella turcica, or as a preventive measure in adrenalectomized patients. Radiation therapy may be performed even if the tumor is not visible at imaging. Patients with Nelson's syndrome (i.e., invasive pituitary macroadenoma in patients submitted to surgical adrenalectomy) also may benefit from radiation therapy. Disadvantages of this treatment are the time lag prior to containment of hypercortisolism (usually 1–2 years) and the high risk of hypopituitarism over time. Ophthalmoplegia, cerebrovascular events and second brain tumors are rarer complications (2.4% risk at 20 years for the latter) of large-field conventional radiotherapy [58, 59]. Different radiation strategies are available [60] and the choice depends on the site and size of the tumor. Proximity to the optic chiasm is a major concern, as at least 2–5 mm distance from the tumor is required to avoid excessive radiation (no greater than 6–14 Gy). Containment of hypercortisolism occurs in 50–83% of adults [61, 62] and up to 80% of children [63] treated with *conventional external beam radiotherapy (CRT)*. Tumors with maximal diameter >3.5 mm are better approached by conventional *large-field fractionated radiotherapy*. Smaller tumors may be treated by *stereotactic radiosurgery* (e.g., gamma knife radiosurgery, linear accelerator (LINAC)-based radiosurgery, proton beam or α particle radiosurgery in single shot or fractionated radiation delivery) with success rates at 2 years ranging from 63% [64] to 83% [65]. Risk of optic chiasm damage, hypopituitarism and second brain tumors is lower using radiosurgery [66]. *Interstitial pituitary irradiation* with yttrium^{90}(Y-90) or gold^{198} (Au-198) achieved long-term remission in over 70% of cases [67, 68] but is no longer in use.

Adrenal surgery

Removal of the adrenal glands is an obligate choice if pituitary-directed treatments failed or are inexpedient and/or steroid synthesis inhibitors yield poor results. Laparoscopic adrenalectomy is nowadays the preferred approach except when expressly contraindicated, e.g. masses greater than 10 cm, morbid obesity and/or coagulopathy. Adrenal glands can be removed in one or two-step procedures and conversion to open surgery may occasionally be required. The advantages of laparoscopy (i.e., low invasiveness, rapid recovery and briefer hospitalization, lower postoperative morbidity and mortality) outweigh the shorter operative time of open surgery with a laparotomic or flank approach. Adrenalectomy resolves hypercortisolism in all patients with Cushing's disease except for rare cases with remnant or ectopic adrenal tissue [69]. Drawbacks of adrenalectomy are compulsory lifelong glico- and mineralocorticoid replacement therapy and the 15–25% risk of aggressive pituitary tumor enlargement, a.k.a. Nelson's syndrome [16, 70). Prophylactic pituitary irradiation is recommended to prevent this fearsome development. Long-term survival rate after adrenalectomy is reportedly lower than in the general population [71].

Medical treatment

Medical therapy [72] is used prior to surgery for first time surgical patients, in surgical failures or disease recurrences, and in patients awaiting the effects of radiation therapy. Drugs are subdivided according to their site of action in pituitary

neuromodulatory drugs, adrenal steroid synthesis inhibitors and glucocorticoid receptor antagonists.

Pituitary neuromodulatory drugs are theoretically the most rational approach to containment of ACTH secretion by the pituitary adenoma but studies using these compounds failed to demonstrate consistent clinical benefits. Serotonin antagonists, e.g., *cyproheptadine*, *methergoline*, *ritanserin* and *ketanserin*, GABA mimetic compounds such as *valproic acid*, the somatostatin analogue *octreotide* and dopamine agonists (*cabergoline* and *bromocriptine*) have all been attempted with mostly unpredictable and short-lived efficacy [73]. Thiazolidinediones (*pioglitazone* and *rosiglitazone*) and *retinoic acid* have recently been proposed on the basis of promising *in vitro* data and clinical studies are currently underway.

Steroid synthesis inhibitors. *Ketoconazole* is the most commonly used compound. It is administered starting with 200 mg/daily and the dosage progressively increased (max. 1200 mg/daily in 2–3 doses) until cortisol secretion normalizes. Untoward effects, such as abdominal discomfort, gynecomastia and liver toxicity, usually resolve upon dosage reduction [74]. Other, less manageable, steroid synthesis inhibitors are *aminoglutethimide*, *metyrapone*, *trilostane* and *etomidate*, the latter available for intravenous administration [75]. Except for etomidate, most series date back to the 1970s and these compounds are not routinely used. *Mitotane* induces adrenal cortex cell death in addition to blocking the first step of cortisol synthesis and has been employed for extended periods in some patients [76]. Low dose regimens (1–2 g/daily) may prove beneficial awaiting the effects of radiotherapy [77] but, as with other steroid synthesis inhibitors, administration of mitotane requires expert handling.

Glucocorticoid receptor antagonists. *Mifepristone* (RU 486) counteracts the biological effects of cortisol by competitive antagonism with the glucocorticoid receptor and has been used in individual patients with severe symptoms of hypercortisolism, in particular acute psychiatric manifestations [78]. In view of the possible problems associated with drug overdosage, this compound has never entered mainstream medical therapy of Cushing's disease.

Treatment strategy

Pituitary surgery is the treatment of choice for patients with pituitary ACTH-secreting adenomas and cure occurs in two-thirds of patients. Cortisol production might be lowered prior to surgery with steroid synthesis inhibitors. Radiation therapy, preferably stereotactic radiosurgery, is usually performed in surgical failures and in tumor regrowths even though it is used as primary treatment in some centres. The extended timeframe for efficacy of radiotherapy mandates adjuvant medical therapy, most often with ketoconazole. Adrenalectomy should be performed if no other therapeutical choices appear feasible. Lastly, Nelson's syndrome should be approached aggressively with surgical debulking and radiotherapy [79] as neuromodulatory drug therapy, i.e. valproic acid [80], cabergoline [81, 82] and octreotide [83] is only occasionally effective.

Criteria for cure

Several criteria for cure of Cushing's disease have been proposed, in particular after pituitary-directed approaches. Biochemical hypoadrenalism (i.e., morning serum cortisol <1.8 μg/dl, 50 nmol/l, 5–14 days after surgery) is necessary according to some authors [84], while others consider normalization of UFC and reinstatement of cortisol circadian rhythmicity or OST suppressibility adequate markers of disease remission [55]. Clinical signs of adrenal insufficiency, such as asthenia, hypotension and skin flaking, provide further evidence of complete tumoral excision. The persistence of high or only modestly reduced UFC levels, conversely, argues for surgical failure. In patients treated with radiation therapy, normalization of UFC, cortisol rhythm and OST suppression in absence of adjuvant medical therapy is considered indicative of disease remission.

Follow-up

Follow-up is mandatory for patients with Cushing's disease, even if postsurgical criteria are indicative of disease remission as relapse may occur; indeed, nearly 25% of patients successfully cured by surgery relapse over the following 10 years [16]. Further, all the previously mentioned clinical complications require close monitoring and/or specific treatment. Predictors of relapse are non-suppressed postoperative serum cortisol levels, brief duration of postsurgical hypoadrenalism [55], ACTH and/or cortisol responsiveness to CRH or desmopressin stimulation after surgery [16, 85] and features of local invasion at pathological examination of the excised specimen [86]. Periodical reassessment of the HPA axis with UFC, cortisol circadian rhythm and/or OST suppression has to be performed and the appearance of alterations substantiated by repeat dynamic testing (CRH or desmopressin) and pituitary imaging. In patients treated by radiotherapy, evaluation of other pituitary secretions, most notably somatotrope, gonadotrope and thyrotrope, is necessary to establish the development of additional pituitary deficiencies. Hypogonadism and hypothyroidism should be corrected appropriately while the need for GH replacement therapy is still debated in adult patients but is often necessary in pediatric patients to achieve target height [87]. Visual field and visual function should be assessed looking for

optic nerve damage. Yearly monitoring of plasma ACTH levels should be performed in adrenalectomized patients and pituitary imaging carried out if hormone levels increase at any time, for early detection of Nelson's syndrome which may occur many years after adrenalectomy [88]. Signs and symptoms of Cushing's disease disappear or abate after remission has been achieved but some facets of end-organ damage may remain, especially in patients with long-standing hypercortisolism. Features of the metabolic syndrome (e.g., hypertension, glucose intolerance or diabetes, dyslipidemia) may persist after cure and the attendant increased cardiovascular risk should be monitored by appropriate procedures, such as echo-Doppler sonography [89]. Osteoporosis recovers slowly and should be assisted by all available means, e.g. biphosphonates, calcium and vitamin D supplements, and close DEXA monitoring [90]. Psychiatric disturbances may be a major complaint in cured patients and should be treated appropriately. Hormonal deficiencies related to hypercortisolism usually recover after remission but may require subsidization. Persistence of hypogonadism after 3 months of cure requires replacement therapy. Normalization of cortisol secretion may also lead to exacerbation of autoimmune disorders, both in the thyroid and in other organs.

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