Cushing's Disease

Authors
Günter K. Stalla, Denis Ciato, Christina Dimopoulou

Affiliation
Department of Clinical Neuroendocrinology, Max Planck Institute of Psychiatry, Munich, Germany

Key words
Cushing's disease, signs and symptoms, diagnostic tests, transsphenoidal surgery, medical therapy, comorbidities

received 14.05.2018
revised 14.07.2018
accepted 26.07.2018

Bibliography
DOI https://doi.org/10.1055/a-0664-7632
Published online: 21.8.2018
Exp Clin Endocrinol Diabetes 2019; 127: 147–155

ISSN 0947-7349

Correspondence
Dr. Christina Dimopoulou
Department of Clinical Neuroendocrinology
Max Planck Institute of Psychiatry, Kraepelinstr. 10
80804 Munich
Germany
Tel.: +49/89/30 62 24 60, Fax: +49/89/30 62 27 4 60
chdimo@hotmail.com

ABSTRACT

Background Despite advances in diagnostic and therapeutic approach, Cushing's disease (CD) presents a challenging situation for the treating physician.

Aims To elucidate current challenges, present strengths and pitfalls of existing diagnostic tests, enlighten the need for new diagnostic approaches, appraise the effects of surgery and available pharmacological agents and identify future perspectives regarding CD.

Materials and methods Systematic search to PubMed and Medline databases for publications mainly over the last five years.

Results Mutations in the ubiquitin specific peptidase 8 gene have been recently identified in functional sporadic corticotroph adenomas causing CD. Since the prevalence of obesity and metabolic syndrome is rapidly increasing, new diagnostic tests are necessary to differentiate these conditions. Next to the traditional tests, a cutoff of preoperative ACTH/cortisol ratio, an ultrasensitive late night salivary cortisol assay and the desmopressin test have been suggested as valid tools for the diagnosis and differential diagnosis of CD. Transsphenoidal surgery with variable remission and recurrence rates presents the treatment of choice for CD. Medical therapy consists of adrenal-targeted drugs e. g. ketoconazole, metyrapone, etomidate and mitotane and pituitary-targeted drugs e. g. pasireotide, cabergoline and retinoic acid.

Conclusions CD is associated to a significant clinical burden, since numerous comorbidities persist after long-term biochemical control. These chronically ill patients show an increased mortality despite disease remission. Clinicians should treat comorbidities aggressively and seek for appropriate consultations. Structured consultation hours and expert excellence networks are needed in order to allow optimal, individualized care for affected patients, reverse increased morbidity and mortality and identify tumor recurrence early.

Abbreviations

ACTH	adrenocorticotropin
BA	bilateral adrenalectomy
BIPSS	bilateral inferior petrosal sinus sampling
BMI	body mass index
CD	Cushing's disease
CRT	conventional photon beam radiotherapy
CS	Cushing's syndrome
CYP11β	11-beta-hydroxylase
CYP17A1	17-alfa-hydroxylase
ECLIA	automated electrochemiluminescence immunoassay
ERCUSYN	European Registry on Cushing's syndrome
GK	GammaKnife
hCRH	human corticotropin-releasing hormone
HDDST	high-dose dexamethasone suppression test
HPA	hypothalamus-pituitary-adrenal
HRQoL	health-related quality of life
LDDST	low-dose dexamethasone suppression test

LINAC SRS	linear LINAC system
LINAC	linear accelerator
LNSC	late-night salivary cortisol
LVP	lysine vasopressin
PMT	preoperative medical treatment
Proton-beam SRS	proton-beam system
PTCOE	Pituitary Tumor Center of Excellence
QoL	quality of life
SCRT	stereotactic conformal radiotherapy
SRS	stereotactic radiosurgery
SRT	stereotactic radiotherapy
SSTR	somatostatin receptor
TS	transsphenoidal surgery
UFC	urinary free cortisol
USP8	ubiquitin specific peptidase 8
VLDL	very-low-density-lipoprotein

Introduction

Cushing's disease (CD) is a rare disorder caused by an adrenocorticotropin (ACTH) secreting pituitary adenoma [1]. If untreated, CD is associated with an increased morbidity and mortality, mostly due to cardiovascular and metabolic comorbidities [2, 3]. Recently, mutations in the ubiquitin specific peptidase 8 (USP8) gene have been identified in functional sporadic corticotroph adenomas causing CD [4–7].

Clinical presentation, differential diagnosis and treatment of CD frequently represent a demanding task for the endocrinologist despite advances in diagnostic testing, surgical techniques and new pharmacological agents [8]. There is consensus that the best care for these patients is provided by an interdisciplinary team composed of dedicated endocrinologists and experienced pituitary surgeons working in collaboration, in a so called Pituitary Tumor Center of Excellence (PTCOE) [9].

Many typical features of hypercortisolism are highly prevalent in the general population and therefore less discriminative for CD diagnosis [10]. Clinical presentation of CD is variable, ranging from mild or subclinical hypercortisolism to moderate or severe hypercortisolism [11]. Three biochemical tests — urinary free cortisol (UFC), plasma cortisol after dexamethasone and/or late night salivary cortisol are needed to distinguish patients with Cushing's syndrome (CS) from those with obesity or metabolic syndrome [12]. Recurrent infections and osteopenia have been reported to be the most discriminant symptoms between obesity or diabetes mellitus and CS [13].

Numerous diagnostic tests are currently available for establishing diagnosis of hypercortisolism as well as for differential diagnosis of CD. However, none of the available diagnostic tests possesses optimal sensitivity and sensibility and according to currently available consensus guidelines, a combination of two or more tests is recommended in order to establish diagnosis [10].

Transsphenoidal surgery (TS) presents the treatment of choice for CD. However, disease persistence and/or recurrence are frequent; in such cases, repeat TS, radiosurgery and/or pharmacological agents might be required [14]. Although numerous agents have been tested for CD, no optimal medical treatment exists so far, treatment side-effects are frequent and disease persistence rates are high. Bilateral adrenalectomy (BA) has proved to be effective and relatively safe in CD patients with persistent disease and/or poor biochemical control [15].

Aim of this review is to elucidate current challenges concerning CD e. g. various clinical presentation according to disease severity, present strengths and pitfalls of existing diagnostic tests, enlighten the need for new diagnostic approaches, appraise the effects of TS and currently available pharmacological agents for CD as well as recognize future perspectives regarding this challenging condition.

Signs & Symptoms

Numerous signs of CD such as buffalo hump, facial fullness, obesity, thin skin, peripheral oedema, acne and hirsutism are common in the general population, whereas signs such as easy bruising, facial plethora, proximal myopathy or proximal muscle weakness, striae rubrae and weight gain with decreasing growth velocity in children belong to the most useful features for diagnosing CD [10]. Central obesity and weight gain represent the most common and often the initial clinical manifestation of hypercortisolism (95 % of patients). Chronic glucocorticoid excess can also lead to skin thinning, easy bruising or purpura resulting from even small traumas and proximal weakness due to muscle wasting. Minor wounds heal slowly and spontaneous tendon ruptures might happen. Other manifestations of CD include facial acne, hirsutism, acanthosis nigricans and hyperpigmentation. Chronic cortisol excess is also characterized by an impaired defence mechanism. Alterations in calcium metabolism result in bone loss, osteoporosis and pathological fractures associated to increased pain [16]. Bone mass can be restored over time after successful treatment for hypercortisolism [17–19].

CD is associated with numerous cortisol-dependent comorbidities such as psychiatric disorders, diabetes, hypertension, hypokalemia, infections, dyslipidemia, osteoporosis, and poor physical fitness, which lead to increased morbidity and mortality [20, 21]. A significant proportion of these comorbidities seem to persist even after long-term disease remission [22–25]. According to the present Endocrine Society Clinical Practice Guideline, effective treatment of CD includes not only the normalization of cortisol levels, but also the normalization of comorbidities via directly treating the cause of CD and by correspondent treatments (e. g. antihypertensives) [26]. All patients should receive monitoring and adjunctive treatment for cortisol-dependent comorbidities throughout their lives until resolution [26]. All comorbidities should be treated aggressively and if necessary, appropriate consultations should be pursued. When CD and associated comorbidities are managed optimally, mortality rates improve; whether they are similar to those of the general population, remains questionable [26].

Direct and indirect effects of cortisol on lipolysis are believed to cause dyslipidemia in CD [27]. CD has been additionally associated with an increased prevalence of thromboembolic complications and a hypercoagulable state [28]. Glucocorticoid excess further predisposes to endocrine changes, including growth hormone deficiency, gonadal dysfunction, mild secondary hypothyroidism and thyroid nodules [29, 30].

Many CD patients (> 70 %) suffer from neuropsychiatric disturbances including major depression, anxiety, personality changes,

mania, psychosis and sleep disorders [31, 32]. Prolonged glucocorticoid hypersecretion exacerbates cognitive aging, including decreased concentration and impaired memory, possibly linked to brain atrophy and low hippocampal volume [33, 34]. Patients with CD display significantly more often anxiety, depression and psychotic symptoms compared to healthy controls [35, 36]. Impaired quality of life (QoL) in active CD is a consistent finding in many studies and has implications for the long-term management of the disease. All health-related quality of life (HRQoL) parameters improve after treatment with TS, thus a stable long-term low QoL remains [37, 38].

Advances in Diagnostic Testing and Need for New Tests

Numerous biochemical tests have been proposed for the diagnosis of hypercortisolism; however, their diagnostic accuracy depends upon etiology of hypercortisolism, patient's comorbidities, robustness of the assays, concomitant medications and the setting of investigations [39].

Patients with multiple features compatible with hypercortisolism should be initially tested with one test of high diagnostic accuracy e. g. UFC, late night salivary cortisol, 1 mg overnight or 2 mg 48-h dexamethasone suppression test. If initial testing is abnormal, patients should receive a second confirmatory test and then undergo testing for the cause of CS [10]. The standard tests to differentiate between CD and ectopic CS comprise the CRH-stimulation test with a sensitivity of 76 % and a specificity of 100 % and the HDDST with a sensitivity of 88 % and a specificity of 90 % [40].

However, diagnostic reality seems to differ from available guidelines, as shown in a recent publication from the European Registry on CS (ERCUSYN) [39]. Of the first-line tests, UFC was performed in 78 % of patients, overnight 1 mg dexamethasone suppression test in 60 % and late-night salivary cortisol in 25 %. Use of high-dose dexamethasone suppression test (HDDST) was slightly more frequent in the last 5 years as compared with previous years. Of the additional tests, late-night serum cortisol was measured in 62 % and 48-h 2 mg/day low-dose dexamethasone suppression test (LDDST) in 33 % of cases. ACTH was performed in 78 % of patients.

As far as CD diagnosis is concerned, a cutoff of preoperative ACTH/cortisol ratio > 2.5 was recently suggested to be diagnostic of CD with a sensitivity of 63 % and a specificity of 82 % [41]. However, this new preoperative ratio is not well established and can be used to diagnose CD only together with other diagnostic tests. Additionally, we have to take into account that the standard CRH-stimulation test with a sensitivity of 76 % and a specificity of 100 % and the HDDST with a sensitivity of 88 % and a specificity of 90 % are rather superior [40]. On the other hand, an ultrasensitive late night salivary cortisol assay by tandem mass spectrometry (LC-MS/MS) was recently found to have diagnostic sensitivity of 100 % and specificity of 92 % - when the cutoff value was 70 ng/dL - in determining patients with CS or CD [42]. The desmopressin test - a vasopressin analogue selective for type 2 vasopressin receptors – has been recently suggested as a valid tool both in the diagnosis and in the follow-up of patients with CD [43].

In the differential diagnosis of ACTH-dependent CS, bilateral inferior petrosal sinus sampling (BIPSS) is useful in cases when there is no obvious source of ACTH hypersecretion, sellar imaging fails to detect small pituitary adenomas or a pituitary incidentaloma might be present [44, 45]. Standardized cut-off value for inferior petrosal sinus to peripheral venous ACTH ≥ 2:1 for the basal and ≥ 3:1 after stimulation are considered to imply a pituitary source of ACTH excess. However, diagnostic errors exist, false negative cases have been described and many patients assumed to have ectopic tumors based upon negative BIPSS remain without diagnosis as described in a retrospective study by Swearingen et al.; the authors report a sensitivity of 90 % with a specificity of 67 % after CRH stimulation [46]. On the other hand, BIPSS using either human corticotropin-releasing hormone (hCRH) or lysine vasopressin (LVP) stimulation confirmed the ACTH source in all patients [47]. BIPSS with desmopressin has been recently proposed as an alternative choice to IPSS with CRH, however with moderate accuracy in tumor lateralization (concordance rate 72.5 %) [48].

Data regarding sensitivity and sensibility of biochemical tests in obese populations are rather conflicting. Recently, sensitivity of the late-night salivary cortisol (LNSC) measured by automated electrochemiluminescence immunoassay (ECLIA) was found to be low in detecting CD in an obese population (BMI ≥ 35 kg/m^2) [49]. An automatic face classification of hypercortisolism by computer software has been even suggested as a novel screening approach in women [50].

In pregnancy, another real medical challenge as far as diagnosis and management of CD are concerned, the hypothalamus-pituitary-adrenal (HPA)-axis undergoes significant changes and symptoms of hypercortisolism are difficult to distinguish from those of pregnancy; on the other hand, there is no consensus regarding the most effective and safe treatment modality under these exceptional circumstances [51].

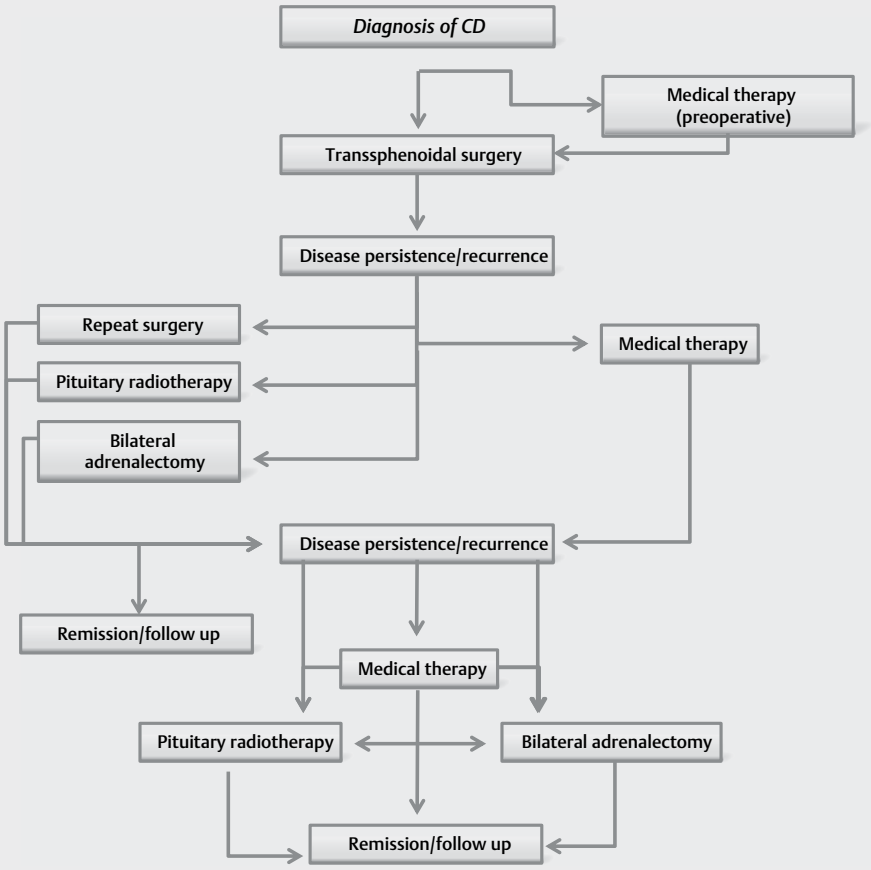
Therapy

Primary goals of CD treatment comprise normalization of cortisol secretion, ablation or disruption of the primary tumor lesion, preservation of the anterior pituitary function and reversal or amelioration of clinical complications. Patients' conditions need to be controlled for a long period of time to prevent recurrence [52, 53]. A multimodal approach is often required to achieve an efficacious disease management [52].

A schematic algorithm for the management of CD is shown in ▶ **Fig. 1**.

Outcome of TS

TS presents the treatment of choice for CD. Remission rates vary dependent on tumor size (65–90 % for microadenomas; < 65 % for macroadenomas), tumor extension, adenoma visibility on magnetic resonance imaging, and neurosurgical expertise [14, 54]. Extensive follow up after TS is essential for at least 10 years due to high recurrence risk of 20–25 % [55–57]. Disease persistence or recurrence requires second-line treatment, which includes repeat surgery, radiotherapy, pharmacological therapy and adrenalectomy. However, none of these alternatives is free of complications. Repeat surgery has generally a lower rate of success than first surgery (50–60 %) and bears an increased risk of pituitary failure [53, 58, 59].



▶ **Fig. 1** Schematic algorithm for the management of Cushing's Disease.

In a single-center experience, 341 patients undergoing first TS had a remission rate of 86 % for macroadenomas and 83 % for microadenomas, lower remission rates for second TS and even lower for patients with invasive tumors [60]; outcomes were obtained with a follow-up length from 12 to 36 months.

We also attempted to describe long-term remission and recurrence rates of CD in a series incorporating different neurosurgeons, trying to reflect care reality in the Munich Metropolitan Region. After first TS, we recorded an overall remission rate of 71 % comparing favorably with the literature; patients with macroadenomas experienced lower remission rates compared to those with microadenomas (69 % vs. 79 %), again in accordance with published series. We documented an overall recurrence rate of 34 %, which falls at the higher end of the published range so far, supporting our study hypothesis (series incorporating different neurosurgeons vs. single-surgeon expert series) [54].

Whether remission and recurrence rates differ according to surgical technique remains under debate. A recently published meta-analysis found no significant difference regarding remission and recurrence rates between patients who underwent endoscopic and those who underwent microscopic TS [61]. Patients with confirmed CD and no adenoma at the time of TS represent an additional challenge for the neurosurgeon. Carr et al. documented a beneficial effect of a two-thirds pituitary gland resection when no adenoma was found at the time of TS [62], while Cebula et al. found no statistical difference between patients with positive or negative MRI [63].

Radiotherapy & bilateral adrenalectomy

Radiotherapy should be considered as second-line treatment for patients with persistent hypercortisolism after pituitary surgery or as a primary treatment in those unfit for surgery. Two different modalities have been employed for radiotherapy in CD patients, named conventional photon beam radiotherapy (CRT) and stereotactic radiotherapy (SRT). CRT was the first radiation treatment available for CD. It consists in delivering radiation treatment with photons generated by a linear accelerator (LINAC) to the target tumor at daily doses over a period of 25–30 days to provide non-tumor cells time to recover between doses [52]. SRT substituted recently CRT, because it can deliver a high dose of radiation to the tumor by minimizing the exposure of surrounding structures [52, 64]. SRT can be delivered as single treatment (stereotactic radiosurgery [SRS], that is safer for tumors distant more than 3–4 mm from the optic apparatus) or fractionated treatment (stereotactic conformal radiotherapy [SCRT]). SRS can be performed with different techniques, including a multiheaded cobalt unit (GammaKnife

▶ **Table 1** Mechanism of action, potential clinical usability and effects of the currently approved drugs for Cushing's Disease.

Drug	Mechanism of action	Potential clinical positioning	Beneficial effects	Side effects	References
Ketoconazole	↓ CYP17, ↓ CYP11 β	Pre-post surgery	Decrease of UFC levels	hepatoxicity	74, 75
Metyrapone	↓ CYP11 β	Pre-post surgery/radiotherapy	Decrease of UFC levels	Adrenal insufficiency, increased androgen levels	76, 77
Etomidate	↓ CYP11 β	For patients not able to take oral medication	Rapid adrenal suppression	Adrenal suppression, decrease in blood pressure, anaphylactic reactions, nausea, vomiting	74 79
Mitotane	↓ CYP11A1, ↓ CYP11 β	Pre-post surgery	Decrease of cortisol production	gastrointestinal, neurological, hepatic disturbances	55, 80
Mifepristone	GR antagonist	Non-responders to multimodal therapy	Decrease body weight, waist circumference and body fat, increased insulin sensitivity	Nausea, fatigue, decrease of blood potassium, headaches, arthralgia, vomiting, endometrial thickening, peripheral edema	74, 81 82
Pasireotide	SSTRs (mainly 5) stimulation	After surgery or in patients not eligible for surgery or with recurrence	Decrease of UFC levels	Glucose-related adverse effects	87-91
Cabergoline	D2 receptor stimulation	Mainly effective in patients with D2 expression	ACTH suppression	Well tolerated in general	52, 94
Retinoic acid	Inhibition of ACTH secretion	Persistent of recurrent hypercortisolism after trans-sphenoidal surgery	Decrease of UFC levels	Potential teratogenicity, mucocutaneous toxicity, liver function abnormalities, conjunctivitis, mucositis and severe photosensitivity	95-97

[GK]), a linear LINAC system [LINAC SRS], or a proton-beam system [Proton-beam SRS] [48, 64]. The latter, has the advantage of redistributing the radiation dose to a three-dimensional target maximizing the exclusion of the surrounding normal tissue [64].

The outcome of radiotherapy in CD is based on control of hormone secretion and tumor growth. A wide experience has been documented with the CRT, and more recently data have been accumulated about SRT. In both cases, remission of hypercortisolism can be reached with a variable interval, and no clear difference in time of decline of cortisol levels was detected so far [64, 66]. However, more long-term follow up studies are needed to detect the possibility of recurrence after SRT [52].

Studies showed that radiotherapy is associated with disease control in an average of 64 % of patients by using CRT and 61 % with different approaches of SRT, and recurrence was reported in around 16 % and 12 % of patients for CRT and SRT, respectively [52]. Despite the efficacy of the treatment, there are severe risks associated that include pituitary failure in 50 % of cases [53], optic neuropathy (1–2 %) and other cranial neuropathies (2–4 %) [65]. Recurrence was in principle reported in patients who received conventional RT [65, 67].

In case of severe and prolonged disease, an additional second-line therapy is represented by BA, which was widely used in the past. A rapid decrease in cortisol levels is obtained, but loss of adrenal function implies a lifelong dependency on glucocorticoid substitution and a risk for developing Nelson´s syndrome [68].

Medical therapy

Medical treatment can be applied at any stage of the disease, even preoperatively to reduce complications, e. g. bleeding tendency [69]. According to ERCUSYN, patients who receive preoperative medical treatment (PMT, 20 %) are more likely to have normal cortisol seven days after surgery [70]. Several molecular targets are currently available, however, there is still little clinical experience [57, 71–75].

Mechanism of action, potential clinical usability and effects of the currently approved drugs for CD are shown in ▶ **Table 1**.

Adrenal-targeted drugs

Adrenal-directed therapy consists of drugs blocking steroidogenesis to control cortisol excess e. g. ketoconazole, metyrapone, etomidate and mitotane. Although generally very effective, they do not target the source of the disease and require close clinical monitoring due to adverse effects, including adrenal insufficiency. Steroidogenesis inhibitors can be applied before and after surgery or radiotherapy, or as bridging therapy till reaching definitive eucortisolism [52, 69, 73].

Ketoconazole is a 17-alfa-hydroxylase (CYP17A1) and 11-beta-hydroxylase (CYP11β) inhibitor; it has been extensively used in CD patients due to its potent and rapid normalisation of UFC levels. However, close liver enzyme monitoring is necessary due to potential hepatotoxicity. Small cohort studies showed UFC normalisation in 30 to 90 % of patients [74]. A retrospective multicenter study showed beneficial effects of ketoconazole even when administered preoperatively (improvement in diabetes, hypertension and hypokalaemia in 50 % of cases). Hepatotoxicity was relatively frequent, but remained moderate [75].

Metyrapone inhibits the final steps of steroidogenesis and is generally used as a second- or third-line agent in CD in combination with other drugs, which may help to ameliorate its side effects. Metyrapone achieved biochemical remission in 83 % of CD patients, who also underwent radiotherapy. The drug was well tolerated [76].

Most common side effects are adrenal insufficiency, acne and hirsutism, hypokalemia, edema, and hypertension [77].

In cases of endocrine cancer-related life-threatening hypercortisolism, combination therapy with metyrapone and ketoconazole has proved to be well tolerated and provides rapid control of hypercortisolism and clinically relevant endpoints [78].

Etomidate is an anesthetic drug, only available for parenteral administration. It has a rapid onset of action and a similar mechanism with that of metyrapone [74]. It can be particularly useful in severely ill hospitalized or psychotic patients (rare phenomenon) to normalise hypercortisolemia rapidly [79]. Side effects include adrenal suppression, hypotension, anaphylactic reactions, nausea and vomiting.

Although mitotane is an adrenostatic drug such as ketoconazole, metopyrone or etomidate, it is above all an adrenolytic agent and therefore primarily suitable for treating patients with adrenocortical carcinoma. A biochemical response in CD patients was recently reported as first- or second line therapy [80]. Since it is very lipophilic, it is mainly stored in the adipose tissue and the brain causing long-lasting gastrointestinal, neurological and hepatic side-effects, and therefore less suitable for treating CD. Mitotane can induce adrenal insufficiency during long-term therapy [55].

Another adrenal-targeted therapeutic concept includes the blockade of glucocorticoid receptor with mifepristone[74]. In the largest prospective study to date, long-term mifepristone treatment increased ACTH in approximately two-thirds of CD patients, with stable ACTH elevations observed within the first week of treatment. Over time, both corticotroph tumor progression and regression occurred, with possible significant increases in ACTH levels without evidence of tumor growth [81]. However, reported side effects include nausea, fatigue, hypokalemia, headaches, arthralgia, vomiting, endometrial thickening and peripheral edema [82]. A limitation of mifepristone is the fact that there is no biochemical marker for its effect; the patient should be substituted with hydrocortisone for safety reasons.

Novel adrenostatic drugs are currently under investigation with promising beneficial effects. LCI699 (Osilodrostat) is an inhibitor of cortisol and aldosterone synthesis [83]. It shares a similar mechanism of action of metyrapone, but being more potent and with a longer half-life. Side effects such as gastrointestinal disturbances followed by headaches have been reported [73]. At present, phase 2 and phase 3 studies are ongoing to test safety and efficacy of the drug in CD [73, 84, 85].

Levoketoconazole (COR-003) acts similarly to its enantiomer, ketoconazole (2 S, 4 R and 2 R,4 S racemic mixture), but has superior effects on the integral enzymes in the cortisol biosynthesis pathway, possibly leading to higher efficacy at lower doses, and fewer adverse side effects [73, 83]. A phase III single-arm, open-label trial (clinicaltrials.gov; NCT01838551) is currently ongoing to evaluate the effects of levoketoconazole in patients with CS [73, 86].

Pituitary directed drugs

Targeting the corticotroph pituitary adenoma can provide a direct effect on the source of the disease. The somatostatin analogue pasireotide has a higher affinity for somatostatin receptor (SSTR) 5, which is the most abundant SSTR in human corticotroph adenomas and was demonstrated to inhibit ACTH secretion and tumor growth both in vitro and in vivo[87, 88]. The drug is approved for CD patients not eligible to surgery or with recurrence. In a phase III study (n = 16, 5 years of pasireotide treatment), median percentage change from baseline in mean UFC was -82.6 % and -81.8 % after 1 and 5 years respectively, while 11 patients had mean UFC ≤ upper limit of normal after 5 years with a similar safety profile at 5 years to that reported after 12 months [89]. In the same study , significant improvements of general signs and symptoms were recorded even without complete UFC normalisation, and hyperglycemia-related events were experienced in 73 % of · patients [90], confirming strong need for frequent blood glucose monitoring [91].

The dopamine agonist cabergoline has been initially tested in CD patients due to the presence of functional D2 receptor in some corticotroph tumors in vitro and in vivo, proving sufficient disease control in approximately 40 % [92, 93]. No important adverse effects were observed [52]. The drug can be used as off label treatment in a small subset of CD patients, depending on tumor size, origin of the corticotroph adenoma or molecular characteristics of the D2 receptor [94].

Retinoic acid showed promising in vitro and in vivo results in terms of inhibition of tumor cell growth and hormone secretion [95, 96]. A key limitation of retinoid therapy is that concentrations required for being effective might cause teratogenicity, mucocutaneous toxicity, liver function abnormalities, conjunctivitis, mucositis and severe photosensitivity. In a proof-of-concept study, 42 % of patients showed UFC decrease or normalization after 6 months; 43 % of patients had full disease control, whereas 29 % had partial disease control. The treatment was generally well tolerated [97].

Conclusions – Future Perspectives

Chronic glucocorticoid excess leads to numerous somatic and psychiatric comorbidities and increased mortality, which often persist despite long-term biochemical control of the disease. Clinicians should treat all comorbidities aggressively and seek for appropriate consultations, if necessary. Genetic and molecular mechanisms responsible for excess ACTH secretion have been identified. New biochemical and imaging approaches as well as progress in surgical and radiotherapy techniques have improved disease management. Development of new pharmacological agents offers physicians additional choices to treat persistent hypercortisolism; however, clinical experience with most of these compounds is limited. The best care for these chronically ill patients is provided by a multidisciplinary team composed of dedicated endocrinologists and experienced pituitary surgeons. The development of expert excellence networks including common databases and biobanking structures facilitates optimal, individualized care for patients affected by this challenging disease. Structured consultation hours are needed in order to reverse increased morbidity and mortality and identify tumor recurrence early.

Conflict of Interest

GS has received consulting honoraria, reimbursement of conferences/educational event fees, travel expenses, and/or study support (third-party funds) from Pfizer, Ipsen, Lilly, Shire, Novartis, Sandoz, NovoNordisk, and HRA. DC and CD have nothing to disclose.

References

[1] Newell-Price J. Cushing's syndrome. Clin Med (Lond) 2008; 8: 204–208

[2] Newell-Price J, Bertagna X, Grossman AB et al. Cushing's syndrome. Lancet 2006; 367: 1605–1617

[3] Pivonello R, Isidori AM, De Martino MC et al. Complications of Cushing's syndrome: State of the art. Lancet Diabetes Endocrinol 2016; 4: 611–629

[4] Perez-Rivas LG, Theodoropoulou M, Ferraù F et al. The Gene of the Ubiquitin-Specific Protease 8 Is Frequently Mutated in Adenomas Causing Cushing's Disease. J Clin Endocrinol Metab 2015; 100: E997–E1004

[5] Reincke M, Sbiera S, Hayakawa A et al. Mutations in the deubiquitinase gene USP8 cause Cushing's disease. Nat Genet. 2015; 47: 31–38

[6] Theodoropoulou M, Reincke M, Fassnacht M et al. Decoding the genetic basis of Cushing's disease: USP8 in the spotlight. Eur J Endocrinol 2015; 173: M73–M83

[7] Perez-Rivas LG, Reincke M. Genetics of Cushing's disease: An update. J Endocrinol Invest 2016; 39: 29–35

[8] Lacroix A, Feelders RA, Stratakis CA et al. Cushing's syndrome. Lancet. 2015; 386: 913–927

[9] Casanueva FF, Barkan AL, Buchfelder M et al. Criteria for the definition of Pituitary Tumor Centers of Excellence (PTCOE): A Pituitary Society Statement. Pituitary 2017; 20: 489–498

[10] Nieman LK, Biller BM, Findling JW et al. The diagnosis of Cushing's syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2008; 93: 1526–1540

[11] Stalla GK, Dimopoulou C. Clinical diagnosis: Signs, symptoms, epidemiology. In: Handbook of Cushing's disease BioScientifica 2011

[12] Loriaux DL. Diagnosis and Differential Diagnosis of Cushing's Syndrome. N Engl J Med 2017; 376: 1451–1459

[13] Schneider HJ, Dimopoulou C, Stalla GK et al. Discriminatory value of signs and symptoms in Cushing's syndrome revisited: What has changed in 30 years? Clin Endocrinol (Oxf) 2013; 78: 153–154

[14] Biller BM, Grossman AB, Stewart PM et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: A consensus statement. J Clin Endocrinol Metab 2008; 93: 2454–2462

[15] Oßwald A, Plomer E, Dimopoulou C et al. Favorable long-term outcomes of bilateral adrenalectomy in Cushing's disease. Eur J Endocrinol 2014; 171: 209–215

[16] Dimopoulou C, Athanasoulia AP, Hanisch E et al. Clinical characteristics of pain in patients with pituitary adenomas. Eur J Endocrinol 2014; 171: 581–591

[17] Scommegna S, Greening JP, Storr HL et al. Bone mineral density at diagnosis and following successful treatment of pediatric Cushing's disease. J Endocrinol Invest 2005; 28: 231–235

[18] Minetto M, Reimondo G, Osella G et al. Bone loss is more severe in primary adrenal than in pituitary-dependent Cushing's syndrome. Osteoporos Int 2004; 15: 855–861

[19] Ohmori N, Nomura K, Ohmori K et al. Osteoporosis is more prevalent in adrenal than in pituitary Cushing's syndrome. Endocr J 2003; 50: 1–7

[20] Mancini T, Kola B, Mantero F et al. High cardiovascular risk in patients with Cushing's syndrome according to 1999 WHO/ISH guidelines. Clin Endocrinol (Oxf). 2004: 61: 768–777

[21] Pivonello R, Faggiano A, Lombardi G et al. The metabolic syndrome and cardiovascular risk in Cushing's syndrome. Endocrinol Metab Clin North Am 2005; 34: 327–339

[22] Feelders RA, Pulgar SJ, Kempel A et al. The burden of Cushing's disease: Clinical and health-related quality of life aspects. Eur J Endocrinol 2012; 167: 311–326

[23] van Haalen FM, Broersen LH, Jorgensen JO et al. Management of endocrine disease: Mortality remains increased in Cushing's disease despite biochemical remission: A systematic review and meta-analysis. Eur J Endocrinol 2015; 172: R14

[24] Colao A, Pivonello R, Spiezia S et al. Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. J Clin Endocrinol Metab 1999; 84: 2664–2672

[25] Berr CM, Stieg MR, Deutschbein T et al. Persistence of myopathy in Cushing's syndrome: Evaluation of the German Cushing's Registry. Eur J Endocrinol 2017; 176: 737–746

[26] Nieman LK, Biller BM, Findling JW et al. Treatment of Cushing's syndrome: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2015; 100: 2807–2831

[27] Arnaldi G, Scandali VM, Trementino L et al. Pathophysiology of dyslipidemia in Cushing's syndrome. Neuroendocrinology 2010; 92: 86–90

[28] Boscaro M, Sonino N, Scarda A et al. Anticoagulant prophylaxis markedly reduces thromboembolic complications in Cushing's syndrome. J Clin Endocrinol Metab 2002; 87: 3662–3666

[29] Arnaldi G, Angeli A, Atkinson AB et al. Diagnosis and complications of Cushing's syndrome: A consensus statement. J Clin Endocrinol Metab 2003; 88: 5593–5602

[30] Invitti C, Manfrini R, Romanini BM et al. High prevalence of nodular thyroid disease in patients with Cushing's disease. Clin Endocrinol (Oxf) 1995; 43: 359–363

[31] Pereira AM, Tiemensma J, Romijn JA. Neuropsychiatric disorders in Cushing's syndrome. Neuroendocrinology 2010; 92: 65–70

[32] Leistner SM, Klotsche J, Dimopoulou C et al. Reduced sleep quality and depression associate with decreased quality of life in patients with pituitary adenomas. Eur J Endocrinol 2015; 172: 733–743

[33] Bourdeau I, Bard C, Noel B et al. Loss of brain volume in endogenous Cushing's syndrome and its reversibility after correction of hypercortisolism. J Clin Endocrinol Metab 2002; 87: 1949–1954

[34] Forget H, Lacroix A, Cohen H. Persistent cognitive impairment following surgical treatment of Cushing's syndrome. Psychoneuroendocrinology 2002; 27: 367–383

[35] Sonino N, Bonnini S, Fallo F et al. Personality characteristics and quality of life in patients treated for Cushing's syndrome. Clin Endocrinol (Oxf) 2006; 64: 314–318

[36] Dimopoulou C, Ising M, Pfister H et al. Increased prevalence of anxiety-associated personality traits in patients with Cushing's disease: A cross-sectional study. Neuroendocrinology. 2013; 97: 139–145

[37] Lindsay JR, Nansel T, Baid S et al. Long-term impaired quality of life in Cushing's syndrome despite initial improvement after surgical remission. J Clin Endocrinol Metab 2006; 91: 447–453

[38] Valassi E, Feelders R, Maiter D et al. Worse Health-Related Quality of Life at long-term follow-up in patients with Cushing's disease than patients with cortisol producing adenoma. Data from the ERCUSYN. Clin Endocrinol (Oxf) 2018

[39] Valassi E, Franz H, Brue T et al. Diagnostic tests for Cushing's syndrome differ from published guidelines: Data from ERCUSYN. Eur J Endocrinol 2017; 176: 613–624

[40] Barbot M, Trementino L, Zilio M et al. Second-line tests in the differential diagnosis of ACTH-dependent Cushing's syndrome. Pituitary. 2016; 19: 488–495

[41] Selek A, Cetinarslan B, Canturk Z et al. The utility of preoperative ACTH/cortisol ratio for the diagnosis and prognosis of Cushing's disease. J Neurosci Rural Pract 2018; 9: 106–111

[42] Sturmer LR, Dodd D, Chao CS et al. Clinical utility of an ultrasensitive late night salivary cortisol assay by tandem mass spectrometry. Steroids. 2018; 129: 35–40

[43] Vassiliadi DA, Tsagarakis S. DIAGNOSIS OF ENDOCRINE DISEASE: The role of the desmopressin test in the diagnosis and follow-up of Cushing's syndrome. Eur J Endocrinol 2018

[44] Oldfield EH, Doppman JL, Nieman LK et al. Petrosal sinus sampling with and without corticotropin-releasing hormone for the differential diagnosis of Cushing's syndrome. New England Journal of Medicine 1991; 325: 897–905

[45] Lopez J, Barcelo B, Lucas T et al. Petrosal sinus sampling for diagnosis of Cushing's disease: evidence of false negative results. Clinical Endocrinology 1996; 45: 147–156

[46] Swearingen B, Katznelson L, Miller K et al. Diagnostic errors after inferior petrosal sinus sampling. J Clin Endocrinol Metab 2004; 89: 3752–3763

[47] Jarial DS, Bhansali A, Gupta V et al. Diagnostic accuracy and comparison of BIPSS in response to lysine vasopressin and hCRH. Endocr Connect. 2018; 7: 425–432

[48] Feng M, Liu Z, Liu X et al. Tumour lateralization in Cushing's disease by inferior petrosal sinus sampling with desmopressin. Clin Endocrinol (Oxf) 2018; 88: 251–257

[49] Aberle J, Schulze Zur Wiesch C, Flitsch J et al. Specificity of late-night salivary cortisol measured by automated electrochemiluminescence immunoassay for Cushing's disease in an obese population. J Endocrinol Invest 2018

[50] Kosilek RP, Schopohl J, Grunke M et al. Automatic face classification of Cushing's syndrome in women - a novel screening approach. Exp Clin Endocrinol Diabetes 2013; 121: 561–564

[51] Caimari F, Corcoy R, Webb SM. Cushing's disease: Major difficulties in diagnosis and management during pregnancy. Minerva Endocrinol. 2018

[52] Pivonello R, De Leo M, Cozzolino A et al. The Treatment of Cushing's Disease. Endocr Rev. 2015; 36: 385–486

[53] Bertagna X, Guignat L. Approach to the Cushing's disease patient with persistent/recurrent hypercortisolism after pituitary surgery. J Clin Endocrinol Metab 2013; 98: 1307–1318

[54] Dimopoulou C, Schopohl J, Rachinger W et al. Long-term remission and recurrence rates after first and second transsphenoidal surgery for Cushing's disease: Care reality in the Munich Metropolitan Region. Eur J Endocrinol 2013; 170: 283–292

[55] Tritos NA, Biller BM. Medical management of Cushing's disease. J Neurooncol. 2014; 117: 407–414

[56] Rutkowski MJ, Flanigan PM, Aghi MK. Update on the management of recurrent Cushing's disease. Neurosurg Focus. 2015; 38: E16

[57] Patil CG, Prevedello DM, Lad SP et al. Late recurrences of Cushing's disease after initial successful transsphenoidal surgery. J Clin Endocrinol Metab 2008; 93: 358–362

[58] Liu JK, Fleseriu M, Delashaw JB Jr et al. Treatment options for Cushing disease after unsuccessful transsphenoidal surgery. Neurosurg Focus. 2007; 23: E8

[59] Benveniste RJ, King WA, Walsh J et al. Repeated transsphenoidal surgery to treat recurrent or residual pituitary adenoma. J Neurosurg. 2005; 102: 1004–1012

[60] Feng M, Liu Z, Liu X et al. Diagnosis and outcomes of 341 patients with Cushing's disease following transsphenoid surgery: A single-center experience. World Neurosurg 2018; 109: e75–e80

[61] Qiao N. Outcome of endoscopic vs microsurgical transsphenoidal resection for Cushing's disease. Endocr Connect 2018; 7: R26–R37

[62] Carr SB, Kleinschmidt-DeMasters BK, Kerr JM et al. Negative surgical exploration in patients with Cushing's disease: Benefit of two-thirds gland resection on remission rate and a review of the literature. J Neurosurg 2017; 1–8

[63] Cebula H, Baussart B, Villa C et al. Efficacy of endoscopic endonasal transsphenoidal surgery for Cushing's disease in 230 patients with positive and negative MRI. Acta Neurochir (Wien) 2017; 159: 1227–1236

[64] Tritos NA, Biller BMK. Update on radiation therapy in patients with Cushing's disease. Pituitary 2015; 18: 263–268

[65] Loeffler JS, Shih HA. Radiation therapy in the management of pituitary adenomas. J Clin Endocrinol Metab 2011; 96: 1992–2003

[66] Colao A, Boscaro M, Ferone D et al. Managing Cushing's disease: The state of the art. Endocrine 2014; 47: 9–20

[67] Mehta GU, Ding D, Patibandla MR et al. Stereotactic radiosurgery for Cushing disease: Results of an international, multicenter study. J Clin Endocrinol Metab 2017; 102: 4284–4291

[68] Reincke M, Ritzel K, Oßwald A et al. A critical reappraisal of bilateral adrenalectomy for ACTH-dependent Cushing's syndrome. Eur J Endocrinol 2015; 173: M23–M32

[69] Feelders RA, Hofland LJ. Medical treatment of Cushing's disease. J Clin Endocrinol Metab 2013; 98: 425–438

[70] Valassi E, Franz H, Brue T et al. Preoperative medical treatment in Cushing's syndrome: Frequency of use and its impact on postoperative assessment: data from ERCUSYN. Eur J Endocrinol 2018; 178: 399–409

[71] Fleseriu M, Petersenn S. New avenues in the medical treatment of Cushing's disease: Corticotroph tumor targeted therapy. J Neurooncol. 2013; 114: 1–11

[72] Cuevas-Ramos D, Fleseriu M. Treatment of Cushing's disease: A mechanistic update. J Endocrinol. 2014; 223: R19–R39

[73] Ciato D, Mumbach AG, Paez-Pereda M et al. Currently used and investigational drugs for Cushing´s disease. Expert Opin Investig Drugs 2017; 26: 75–84

[74] Hamrahian AH, Yuen KC, Hoffman AR. AACE Neuroendocrine And Pituitary Scientific Committee. AACE/ACE Disease State Clinical Review: Medical Management of Cushing Disease. Endocr Pract. 2014; 20: 746–757

[75] Castinetti F, Guignat L, Giraud P et al. Ketoconazole in Cushing's disease: Is it worth a try? J Clin Endocrinol Metab 2014; 99: 1623–1630

[76] Verhelst JA, Trainer PJ, Howlett TA et al. Short and long-term responses to metyrapone in the medical management of 91 patients with Cushing's syndrome. Clin Endocrinol (Oxf) 1991; 35: 169–178

[77] Fleseriu M, Petersenn S. Medical management of Cushing's disease: What is the future? Pituitary. 2012; 15: 330–341

[78] Corcuff JB, Young J, Masquefa-Giraud P et al. Rapid control of severe neoplastic hypercortisolism with metyrapone and ketoconazole. Eur J Endocrinol 2015; 172: 473–481

[79] Preda VA, Sen J, Karavitaki N et al. Etomidate in the management of hypercortisolaemia in Cushing's syndrome: A review. European Journal of Endocrinology 2012; 167: 137–143

[80] Baudry C, Coste J, Bou Khalil R et al. Efficiency and tolerance of mitotane in Cushing's disease in 76 patients from a single center. Eur J Endocrinol 2012; 167: 473–481

[81] Fleseriu M, Findling JW, Koch CA et al. Changes in plasma ACTH levels and corticotroph tumor size in patients with Cushing's disease during long-term treatment with the glucocorticoid receptor antagonist mifepristone. J Clin Endocrinol Metab 2014; 99: 3718–3727

[82] Guelho D, Grossman AB. Emerging drugs for Cushing's disease. Expert Opin Emerg Drugs 2015; 20: 463–478

[83] Cuevas-Ramos D, Lim DST, Fleseriu M. Update on medical treatment for Cushing's disease. Clin diabetes Endocrinol 2016; 2: 16

[84] ClinicalTrials.gov [Internet]. Safety and Efficacy of LCI699 for the Treatment of Patients with Cushing's Disease https://clinicaltrials.gov/ct2/show/NCT02180217?term = lci + 699&cond = Cushing + Disease&rank = 1

[85] ClinicalTrials.gov [Internet]. Safety and Efficacy of LCI699 in Cushing's Disease Patients https://clinicaltrials.gov/ct2/results?cond = Cushing + Disease&term = lci + 699&cntry = &state = &city = &dist =

[86] Salvatori R, DelConte A, Geer EB et al. An open-label study to assess the safety and efficacy of levoketoconazole (COR-003) in the treatment of endogenous Cushing's syndrome. Adrenal Tumors, Glucocorticoid Regulation and Action San Diego 2015; FRI-376

[87] Castillo V, Theodoropoulou M, Stalla J et al. Effect of SOM230 (pasireotide) on corticotropic cells: Action in dogs with Cushing's disease. Neuroendocrinology. 2011; 94: 124–136

[88] Hofland LJ, van der Hoek J, Feelders R et al. The multi-ligand somatostatin analogue SOM230 inhibits ACTH secretion by cultured human corticotroph adenomas via somatostatin receptor type 5. Eur J Endocrinol 2005; 152: 645–654

[89] Petersenn S, Salgado LR, Schopohl J et al. Long-term treatment of Cushing's disease with pasireotide: 5-year results from an open-label extension study of a Phase III trial. Endocrine 2017; 57: 156–165

[90] Pivonello R, Petersenn S, Newell-Price J et al. Pasireotide treatment significantly improves clinical signs and symptoms in patients with Cushing's disease: Results from a Phase III study. Clin Endocrinol (Oxf) 2014; 81: 408–417

[91] Colao A, De Block C, Gaztambide MS et al. Managing hyperglycemia in patients with Cushing's disease treated with pasireotide: Medical expert recommendations. Pituitary 2014; 17: 180–186

[92] Pivonello R, Matrone C, Filippella M et al. Dopamine receptor expression and function in clinically nonfunctioning pituitary tumors: Comparison with the effectiveness of cabergoline treatment. J Clin Endocrinol Metab 2004; 89: 1674–1683

[93] Castillo VA, Gómez NV, Lalia JC et al. Cushing's disease in dogs: Cabergoline treatment. Res Vet Sci 2008; 85: 26–34

[94] Pivonello R, Ferone D, de Herder WW et al. Dopamine receptor expression and function in corticotroph pituitary tumors. J Clin Endocrinol Metab 2004; 89: 2452–2462

[95] Páez-Pereda M, Kovalovsky D, Hopfner U et al. Retinoic acid prevents experimental Cushing syndrome. J Clin Invest 2001; 108: 1123–1131

[96] Castillo V, Giacomini D, Páez-Pereda M et al. Retinoic acid as a novel medical therapy for Cushing's disease in dogs. Endocrinology. 2006; 147: 4438–4444

[97] Pecori Giraldi F, Ambrogio AG, Andrioli M et al. Potential role for retinoic acid in patients with Cushing's disease. J Clin Endocrinol Metab 2012; 97: 3577–3583