Chapter 1

Introduction
Cushing's Syndrome

Endogenous Cushing's syndrome is a clinical state resulting from prolonged, inappropriate exposure to excessive secretion of cortisol (1). The syndrome has been named after Harvey Cushing, a neurosurgeon, born in 1869, trained at Johns's Hopkins Medical School and professor at the Peter Brigham Hospital in Harvard from 1912 to 1932 (2). From 1932 until his death in 1939, he worked as professor of neurology at Yale. In 1912, Harvey Cushing described a woman with a syndrome of painfull obesity, hypertrichiosis and amenorrhea, but the cause of this syndrome was not recognized. It was only twenty years later, in 1932, that he described a series of patients with the same symptoms, who, at postmortem examination were found to have a tumor of the pituitary gland. In retrospect, the first case of a patient with Cushing's syndrome has probably been described by William Osler, professor of surgery at John's Hopkins University, in 1899 (3,4).

The title of the paper was “An acute myxoedematous condition, with tachycardia, glycosuria, melaena, mania and death”, describing a case of a 37-year old male patient. A striking clinical feature was a gain in weight of 17 kg in 3 months, which apparently led Osler to consider the diagnosis of acute myxedema, and treat the patient with thyroid-grains. However, in the same report Osler points out a group of clinical symptoms not been reported before, including abdominal fat accumulation, reddish-purple striae and a bloated face. The patient died shortly after presentation. Unfortunately, post-mortem examination was not performed. Interestingly, in 1899, at the time of this case, Harvey Cushing worked as a resident at John’s Hopkins under mentorship of William Osler. There is, however, no evidence that the two ever discussed the case (4).

Several other classic papers have documented patients suffering from symptoms of hypercortisolism, including a paper by Achard and Thiers, who under the title “diabete des femmes a barbe”, describe a series of patients with hirsutism, glycosuria and adrenal lesions at autopsy (5).

In classical cases, the clinical features of Cushing’s syndrome are the triad of obesity, hypertension and diabetes mellitus(6). In general, the clinical picture may vary considerably, with a variety of symptoms associated with hypercortisolemia including weight gain, lethargy, weakness, menstrual irregularities, loss of libido, depression, hirsutism, acne, purplish skin striae, thinned skin and hyperpigmentation (7).

Biochemically, Cushing's syndrome is characterized by loss of the normal feedback mechanism of the hypothalamo-pituitary-adrenal (HPA)-axis and the normal circadian rhythm of cortisol secretion. The etiology of Cushing's syndrome is classically divided in ACTH-dependent and ACTH-independent causes (table 1) (1). ACTH-dependent Cushing's syndrome is usually caused by excessive ACTH production from an adenoma in the pituitary gland, or, more rarely, by ectopic ACTH secretion from a non-pituitary tumor. ACTH-independent Cushing's syndrome is caused by excessive secretion of cortisol by an adrenocortical adenoma or carcinoma, or, rarely, micro- or macronodular bilateral adrenal hyperplasia.
Table 1: Causes of Cushing’s syndrome

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percent of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACTH-dependent Cushing’s syndrome</strong></td>
<td></td>
</tr>
<tr>
<td>Pituitary adenoma (Cushing’s disease)</td>
<td>68</td>
</tr>
<tr>
<td>Ectopic ACTH production</td>
<td>12</td>
</tr>
<tr>
<td>Ectopic CRH production</td>
<td>&lt; 1</td>
</tr>
<tr>
<td><strong>ACTH-independent Cushing’s syndrome</strong></td>
<td></td>
</tr>
<tr>
<td>Adrenal adenoma</td>
<td>10</td>
</tr>
<tr>
<td>adrenal carcinoma</td>
<td>8</td>
</tr>
<tr>
<td>Micronodular hyperplasia</td>
<td>1</td>
</tr>
<tr>
<td>Macronodular hyperplasia</td>
<td>1</td>
</tr>
</tbody>
</table>


UNRESOLVED ISSUES IN CUSHING’S SYNDROME

Since 1932, Harvey Cushing’s description of the syndrome that results from long-term glucocorticoid-excess has not improved upon, but our understanding of its pathophysiologic features and our ability to diagnose and treat the disorder have increased dramatically (7). However, more than in any other area of clinical endocrinology, diagnosis, differential diagnosis and management continue to challenge the physician and occasionally cause considerable controversy. This is reflected by our limited understanding of the biology of the different causes of Cushing’s syndrome and the intrinsic limitations of practically every diagnostic test used in the diagnosis of Cushing’s syndrome in clinical practice (8-13). Finally, once a definitive diagnosis of the cause of Cushing’s syndrome has been made, there is frequently not a simple, straightforward surgical and/or medical treatment available, that can cure the disease without inducing (permanent) side-effects or necessitating additional treatment (14-22). Moreover, even after initial succesfull treatment, recurrence of the disease can occur in a significant number of patients (23-30).

In the following paragraphs, several unresolved issues in Cushing’s syndrome will be discussed, especially concerning the characterization of temporal changes in hormonal secretion, diagnostic problems involved in Cushing’s syndrome, treatment of pituitary-dependent Cushing’s disease and its complications, assessment of cure and risk of relapse after treatment of Cushing’s disease and finally quality of life after succesfull treatment of Cushing’s disease.
CHARACTERIZATION OF TEMPORAL CHANGES IN HORMONAL SECRETION

Cushing’s syndrome is the result of chronic exposure to excess of cortisol, released from the zona reticularis of the adrenal cortex (31). In healthy subjects, cortisol is released episodically. The main rhythm is circadian, in which cortisol level is at its peak around the time of awakening (around 07:00 am) and at its nadir around midnight (32-34). The adrenals are under feed-back control of the hypothalamo-pituitary adrenal (HPA) axis. Figure 1 shows the normal regulation of the HPA axis. In the hypothalamus, the suprachiasmatic nucleus harbours the regulation of the circadian rhythm. From this nucleus, neuronal input activates the paraventricular nucleus, where CRH is released into capillaries in the median eminence, draining into the anterior pituitary through the portal veins. In the anterior pituitary, CRH stimulates ACTH release from the corticotroph cells. Subsequently, ACTH binds to its receptor on the adrenals, resulting in cortisol-release. Finally, ACTH release from the pituitary corticotrophs is inhibited through glucocorticoid feedback, which causes cortisol released from the adrenals to ultimately restrain its own release.

In addition to the circadian changes in cortisol secretion, cortisol is secreted in an episodic, pulsatile fashion (35). This temporal architecture of plasma hormone secretion constitutes an additional mechanism, which may modulate signal transduction and which may also prevent down-regulation of the response of the target organ. In general, the sensitivity for pulsatile regulation within the hypothalamo-pituitary-adrenal axis may not be similar for each level of this axis. For instance, ACTH secretion is more sensitive for pulsatile than for continuous administration of ovine CRH (36). Cortisol secretion is hardly dependent on the pulsatile characteristics of ACTH release, because cortisol levels are similar after prolonged continuous and intermittent ACTH administration. This is not true for another, indirect biological effect of ACTH, like aldosterone secretion. Pulsatile ACTH administration results in higher aldosterone levels than continuous ACTH secretion (37). Finally, at present it is unclear to which extent the biological effects of cortisol are dependent on pulsatile characteristics of cortisol secretion.

For the corticotropic axis, the pulsatile release of ACTH and cortisol is altered in several conditions. In major depression, ACTH pulse frequency was increased, and the nadir of cortisol secretion occurred 3 hours earlier compared to healthy subjects (38,39). In women with the polycystic ovary syndrome, the amplitude of ACTH-pulses at night appeared to be increased. In addition, daytime cortisol secretion was more disorderly compared to controls (40).

The physiological relevance of the pulsatile release of pituitary hormones in general is also clearly demonstrated for the gonadotropic axis in women, where changes in the release pattern of the gonadotropins and gonadal steroids are mandatory for maintaining a normal menstrual cycle (41,42). In men, puberty can only be induced by pulsatile GnRH therapy, thereby underlining the importance of a properly functioning GnRH oscillator (43). Finally, for the somatotropic axis, pulsatile release is also of physiological importance, as shown by studies in
growth-hormone deficient children, where a greater response in growth rate was demonstrated with a more frequent regimen of GH injections than with the same total but weekly dose (44,45).

Figure 1. The hypothalamic–pituitary–adrenal control system.

Neural pathways into the paraventricular nucleus of the hypothalamus can be classified as “stress” inputs (for example, hypoglycemia) directly and through the hippocampus and daily rhythm input (circadian rhythm). These inputs result in an activation of parvocellular neurons that release corticotrophin-releasing factor (CRH) and arginine vasopressin (AVP) into the capillary plexus of the median eminence, which forms long portal veins. These drain into the anterior pituitary, where CRH and AVP influence the corticotrophs to increase release of adrenocorticotropic hormone (ACTH). The hormone enters the systemic circulation and stimulates the adrenal cortex to increase cortisol production. Cortisol exerts its biological effects through the glucocorticoid receptor. Plasma cortisol also drains to saliva and the urine. The hypothalamic–pituitary–adrenal axis loop is completed through glucocorticoid-negative feedback exerted at the anterior pituitary, hypothalamus, and hippocampus. Diagnostic tests associated with each physiologic process are shown in pink. CBG = corticosteroid-binding globulin; CS = Cushing syndrome.

Changes in the pulsatile release of hormones are also observed in patients with various endocrine diseases, including pituitary diseases and non-pituitary-diseases (46-50). In general, in these disease-states, the augmented hormonal release is due to an increase in the amount secreted per burst and/or an increase in pulse frequency. In addition, the orderliness of hormonal secretion is frequently disrupted (48,51,52).

As for Cushing’s syndrome, studying the pathophysiology of episodic hormonal secretion can help understanding the biology of possible causes of hypercortisolism, and may be even exploited as a diagnostic tool (33). From studies in patients with pituitary-dependent Cushing’s disease it appeared that hypercortisolism is characterized by increased basal and increased pulsatile cortisol secretion due to an increased number of pulses and an increased mass secreted per pulse (53). Furthermore, the cortisol-secretion pattern showed more disorderliness compared to healthy controls (54,55,55). At present, it is unclear to which extent the cortisol secretory patterns are different among the different causes of Cushing’s syndrome, especially in primary adrenal Cushing’s syndrome.

In young patients, who still have open epiphysial growth plates, it is well known that the occurrence of Cushing’s syndrome precipitates an inhibition in growth and a decreased final height. Pulsatile growth hormone secretion was shown to be preserved in Cushing’s disease, except for severe hypercortisolism. In addition, secretion of GH was remarkably disorderly in patients with Cushing’s disease (56). However, it is unclear to which extent these changes are related to excess cortisol concentrations per se, rather than to changes within the pituitary associated with the consequences of an ACTH producing pituitary adenoma. At present, however, there is no detailed information available on the secretory profile GH in ACTH-independent Cushing’s syndrome, which could contribute to the understanding of the regulation of growth hormone secretion in conditions of cortisol excess.

Nelson’s syndrome was first described in 1958 as the constellation of a pituitary macroadenoma, markedly elevated ACTH concentrations, and hyperpigmentation of the skin in a patient after bilateral adrenalectomy for pituitary-dependent hypercortisolism (Cushing’s disease) (122). The syndrome develops in 8 - 38% of adults requiring bilateral adrenalectomy for Cushing’s disease (123,124) and occurs infrequently in patients aged 40 yr or more at the time of bilateral adrenalectomy, in contrast to patients treated at an early age (125).

Cushing’s disease and Nelson’s syndrome are considered to be distinct pathological presentations of the same primary biological entity. For example, impaired responsiveness to glucocorticoid enforced negative feedback on ACTH is common to both (126). In addition, under in vitro conditions the secretion of POMC-derived peptides was similar in tumoral tissue derived from patients with Cushing’s disease and Nelson’s syndrome (127). However, CRH infusion stimulates greater and prolonged ACTH secretion in patients with Nelson’s syndrome than Cushing’s disease (128). The pathogenetic mechanisms underlying tumorigenesis and unrestrained ACTH secretion in Nelson’s syndrome are not well understood.
Quantitative comparisons of neurosecretory control of tumoral ACTH secretion in Nelson’s syndrome and Cushing’s disease have not been reported, but could shed light on the pathophysiology of these two clinical entities.

The pulsatile and diurnal changes in release of ACTH- and cortisol (as well as other pituitary hormones) can be studied by frequent sampling of plasma in combination with mathematical tools to analyze the respective secretion patterns. Multiparameter deconvolution analysis is a technique which resolves the serum hormone concentration profile into its constituent secretory contributions and simultaneously estimates the hormone half-life. This analysis can be used to quantify underlying basal and pulsatile hormone secretion and to estimate the corresponding (endogenous) half-life (57). The orderliness of hormone release patterns over 24 h can be quantitated by approximate entropy (ApEn) analysis. ApEn provides a scale-invariant and model-independent quantitation of relative disorderliness, in which higher ApEn values denote greater relative disorderliness or reduced regularity of the release process (58,59). Finally, cosinor analysis can be used to study twenty-four-hour variations in hormonal concentrations, with quantitation of the 24-h cosine amplitude (50% of the nadir-zenith difference), mesor (rhythmic mean) and acrophase (clock-time of maximal value) (60).

**DIAGNOSIS OF CUSHING’S SYNDROME**

In patients with severe clinical symptoms of hypercortisolism, the pretest likelihood of the presence of Cushing’s syndrome is high and the positive predictive value of the biochemical tests is high. Therefore, in these severe cases, the biochemical confirmation usually offers no specific problems. However, it can be difficult to distinguish between mild forms of Cushing’s syndrome and situations referred to as pseudo-Cushing states, such as the metabolic syndrome, depression and alcoholism. In these conditions the pretest likelihood of the presence of disease is low and the positive predictive value of the biochemical tests is negatively affected. This may often lead to confusing results of biochemical tests. Since Cushing’s syndrome is associated with considerable morbidity and mortality and correction of hypercortisolism may substantially improve the metabolic consequences of excess cortisol, even a low index of suspicion should mandate at least a screening evaluation for Cushing’s syndrome. Consequently, with increasing awareness among doctors and the widespread availability of biochemical testing, patients are screened in an earlier phase of their disease, in which only minor abnormalities of cortisol secretion are present, making biochemical conformation even more difficult.

There are several diagnostic tools available for the biochemical screening for hypercortisolism. However, as will be discussed below, no test can be used as a single screening test for the detection of CS, since every test has its specific limitations in sensitivity and specificity.
Introduction

Twenty-four hour urine collection for the measurement of urinary free cortisol (UFC) has been considered a gold standard for the diagnosis of CS (1). However, this method has several limitations, including the influence of fluid intake and impaired renal function, false elevation by specific medications (e.g., carbamazepin and digoxin), mild elevations in pseudo-Cushing’s states and pregnant women, and normal values in mild, subclinical Cushing’s syndrome (61). For these reasons, UFC cannot be considered as a universal single screening test for the detection of Cushing’s syndrome.

The low-dose dexamethasone suppression test (DST) is the second screening test and is based on the assumption that in patients with CS, the negative feedback by glucocorticoids on the hypothalamic-pituitary-adrenal (HPA) axis is diminished. In the classical two-days DST, the suppression of urinary 17-hydroxycorticosteroids was used as an indicator of cortisol suppression (62). Measurement of serum cortisol at 09:00 after the administration of 0.5 mg dexamethasone every 6 h for 48 h and a cut-off value of 50 nmol/l has been reported to have a sensitivity of 98% in the diagnosis of Cushing’s syndrome (63). The overnight low-dose DST consists of the oral intake of 1 mg dexamethasone at 2300 h, and the measurement of fasting plasma cortisol concentration between 0800 and 0900 h the following morning. The international consensus on the criterion for normal level of suppression, has recently been lowered to 50 nmol/l (31), increasing the sensitivity of this test, obviously at the cost of lower specificity. The specificity is further reduced by other interfering factors, such as increased concentrations of cortisol binding globulin, acute and chronic illness, pseudo-Cushing states, decreased dexamethasone absorption and drugs enhancing hepatic dexamethasone metabolism (phenytoin, carbamazepin, rifampicin). In addition, feedback-sensitivity to glucocorticoids varies between subjects, explained by polymorphisms in the glucocorticoid receptor gene (64,65). For these reasons, DST cannot adequately distinguish all patients with Cushing’s syndrome from other subjects.

The third screening test for hypercortisolism is measurement of midnight serum cortisol concentration. In healthy subjects, serum cortisol concentrations follow a circadian rhythm, with a peak at 0700 – 0900 h and falling levels thereafter until a subsequent rise at 0300 – 0400 h (66). In Cushing’s syndrome, several studies have suggested a loss of this circadian rhythm (67-71). However, other and more recent studies have shown that the diurnal pattern of cortisol secretion is preserved in certain patients but with levels that are set abnormally high (46,72-75). At midnight, the overlap of serum cortisol levels between patients with Cushing’s syndrome and the normal range was shown to be minimal (76). Therefore, measurement of midnight serum cortisol levels could be a useful tool in identifying patients with Cushing’s syndrome.

In two studies, the measurement of midnight serum cortisol concentration in the documentation of hypercortisolism was studied (63,77). In both studies, a single midnight serum cortisol value correctly identified almost all subjects with Cushing’s syndrome. The discrepancy in cut-off levels between these studies (> 50 nmol/l and
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> 207 nmol/l respectively) is explained by the fact that in the first study, patients had to be asleep before taking a midnight blood sample (63), while in the second study patients were awake. However, the need for hospitalization to obtain an unstressed midnight blood sample for the measurement of serum cortisol makes this a very impractical test for the primary assessment of hypercortisolism, unsuitable for daily clinical practice.

- The fourth screening test is the measurement of late-night cortisol-concentrations in saliva. Measurement of salivary cortisol concentration has been described since the early 70's (78-80). Salivary cortisol is a valid indicator of the plasma free cortisol concentration and is not affected by the rate of saliva production (81,82). An increase in plasma cortisol is reflected by a change in salivary cortisol concentration within a few minutes. The circadian rhythm of plasma cortisol is similarly reflected in the diurnal variation of salivary cortisol concentration, with a peak in the early morning and nadir around midnight (82,83). The concentration of cortisol in saliva is about 5% of the total plasma cortisol concentration, making the sensitivity of a salivary cortisol assay a very important issue.

The study of Laudat et al. was among the first to document the effectiveness of diurnal salivary cortisol sampling to diagnose CS, with an elevated salivary cortisol level in all patients with CS (83). Since that study, new assay technologies in measuring cortisol concentration in saliva have emerged and several clinical studies have been performed using salivary cortisol as a first line test in screening for CS (84-90). In all studies, late-night salivary cortisol-concentration performed well in establishing hypercortisolism, with sensitivity and specificity ranging from 92 – 100%. However, these studies have mostly been performed in a research setting, with in-patients, under ideal conditions to accomplish the desired outcome. Moreover, patient series in all studies were referral-based samples, introducing possible selection bias. Finally, different cut-off levels of salivary cortisol for the diagnosis of CS were reported, ranging from > 3.6 nmol/l to > 15.2 nmol/l, at least partly explained by the use of different assays.

In patients with equivocal results, a combined dexamethasone suppression-test and CRH-test can be performed. This test was shown by one center to be highly accurate in distinguishing patients with CS from subjects with pseudo-CS (91,92).

If CS is confirmed by one or more of the screening tests, determination of plasma ACTH values is the next step to establish the cause of hypercortisolism (66). ACTH concentrations below the level of detection or below 2 pmol/l suggest an ACTH-independent cause of CS (93). Plasma ACTH concentrations greater than 4 pmol/l are compatible with an ACTH-dependent cause. However, ACTH-levels may not be fully suppressed in some patients with CS and intermittent or moderate hypercortisolism. In these cases, a CRH stimulation test is indicated, with measurement of plasma ACTH (31).
If ACTH is suppressed, the next step is computed tomography (CT) and/or magnetic resonance imaging (MRI) to identify the type of adrenal lesion(s) responsible for CS.

In patients with ACTH-dependent CS, a pituitary MRI with gadolineum enhancement should be performed, which has a sensitivity ranging from 50-60% in identifying a pituitary adenoma (94,95). In patients without a clear pituitary adenoma on MRI, bilateral inferior petrosal sinus sampling (BIPSS) should be performed to establish the source of ACTH secretion. An inferior petrosal sinus (IPS) to peripheral ACTH ratio greater than 2.0 in the basal state, and/or a ratio greater than 3.0 after CRH stimulation is consistent with pituitary-dependent Cushing’s disease (96). However, false-negative results may occur, due to technical factors as well as anomalous venous drainage(31). Also, false-positive results can be obtained in rare cases of ectopic CRH secreting tumors (97).

In conclusion, the biochemical confirmation of CS remains a challenge to the clinician, with limitations of every test employed. Measurement of late-night salivary cortisol concentration appears to be a promising, patient-friendly additional test in this challenging field.

**TREATMENT: TRANSSPHENOIDAL SURGERY AND COMPLICATIONS**

Transphenoidal surgery (TSS) is the treatment of choice for most lesions in the sellar region. Disadvantages of the transphenoidal approach are a restricted field of surgery and generally absent visualization of the optic nerves. In experienced hands, it is a safe procedure with low morbidity and mortality rates. In a large national survey in the USA among 958 neurosurgeons performing transphenoidal operations, the mean operative mortality was 0.9% (98). Postoperative anterior pituitary insufficiency (19.4%) and diabetes insipidus (17.8%) were complications with the highest incidence of occurrence.

Pituitary adenomas originate below the diaphragma sellae, and, thus, outside the arachnoid membrane and the subarachnoid space. Therefore, the transphenoidal removal of a pituitary tumor usually can be performed entirely outside the arachnoid membrane. However, the arachnoid membrane can be injured and penetrated in the process of opening the dura (in the case of a low-situated anterior arachnoid recess), maneuvers in the anterior-superior aspect of the sella-exposure or removal of a macroadenoma, when the distended elevated arachnoid membrane begins to invert into the sella. A subsequent CSF fistula exposes the patient to the risk of developing postoperative meningitis. The incidence of CSF fistula in the earlier mentioned national survey was 3.9% and of meningitis 1.5% (98). In the literature, the incidence of postoperative meningitis ranges from 0.4% to 9% (21).

The management of intraoperative CSF leakage consists primarily of meticulous, watertight reconstruction of the sellar floor. Several techniques of sella closure have been described in the literature. In addition, an external lumbar drain (ELD) can be
inserted to prevent postoperative rhinorrhea and fistula formation, a method which is employed by some, but rejected by others (99-102). However, the effect of ELD insertion on the risk of postoperative meningitis, has not been described yet.

POSTOPERATIVE EVALUATION AND FOLLOW-UP

Although TSS allows cure of Cushing’s disease, the reported success rates vary from 50 to almost 90% (103-107). The skill and experience of the neurosurgeon is a very important factor determining this outcome of TS (18). Additional factors determining the high variability in success rate are differences in criteria used to define remission and differences in duration of follow up, which may result in a low rate of late relapses during short-term follow up.

Immediate postoperative assessment of outcome of pituitary surgery is important in order to plan further treatment in patients with persistent hypercortisolism.

For the assessment of cure after pituitary surgery for Cushing’s disease, several methods have been used. First, unmeasurable postoperative fasting serum cortisol levels appears to be a valuable indicator for remission. This is explained by suppression of non-tumorous corticotrophs by longstanding exposure to elevated levels of glucocorticoids. Histologically, this is characterized by so called Crooke’s hyaline atrophy (108). However, with measurable serum cortisol levels, long-term remission is also possible (109). Similarly, determination of the 24-hour urinary cortisol excretion has not much practical value in the assessment of cure after pituitary surgery for Cushing’s disease. Finally, failure to suppress with 1 mg dexamethasone in the early postoperative period, is not necessarily associated with surgical failure (110).

Early postoperative assessment is also valuable as an early marker of the risk of relapse of Cushing’s syndrome. In this respect, an undetectable postoperative fasting serum cortisol is not always associated with long-term remission (23,111). Similarly, 24-hour urinary cortisol excretion cannot identify patients at risk for relapse. In several studies, the role of CRH testing in the early postoperative period for the assessment of risk for relapse in Cushing’s disease has been evaluated. Subjects with a subnormal cortisol and/or ACTH response to CRH generally remain in remission, however again with exceptions.

The metyrapone test was introduced 35 years ago to assess the functional capacity of the hypothalamo-pituitary-adrenocortical axis. Since then, it has been used widely for this purpose. It has also been used for the differential diagnosis of Cushing’s syndrome. Until recently, the metyrapone test has not been used in the early postoperative assessment after TSS for Cushing’s disease.

The rate of recurrence of Cushing’s disease depends on the criteria for initial cure, and varies from 5 to 24% in the literature (23,24,111-113). When pituitary surgery has failed to cure Cushing’s disease or in case of recurrence of Cushing’s disease, there are several options for further treatment. Pituitary irradiation is nowadays
considered as the most appropriate treatment in these cases (24). Newer techniques of stereotactic radiotherapy, such as gammaknife radiosurgery, might even improve the outcome, but experience and follow-up time are still limited (114-118). Medical treatment has the major major disadvantage of the need for lifelong therapy, but can be used to overcome the waiting-time for the effect of radiotherapy. Steroidogenesis inhibitors, including ketoconazole, metyrapone and mitotane are effective in a majority of patients (119). Compounds modulating ACTH release from a pituitary tumor, such as dopamine-agonists, PPAR-gamma agonists, and somatostatin analogs are interesting agents that need further investigation (120,121).

Bilateral adrenalectomy is another option in patients with persistent or recurrent Cushing’s disease, especially in patients with severe hypercortisolism that requires prompt reversal or after failure of radiotherapy. Disadvantages are the need for life-long replacement-therapy with gluco- and mineralocorticoids, the risk of acute adrenal insufficiency and the risk of development of Nelson’s syndrome.

QUALITY OF LIFE

TSS allows cure of Cushing’s disease in a large proportion of patients, whereas pituitary irradiation and/or bilateral adrenalectomy can correct hypercortisolism in the remaining patients. Despite this excellent prognosis (from a hormonal perspective), physical recovery is remarkably slow and often incomplete, with residual impairments such as osteoporosis, hypertension and pituitary deficiencies. Similarly, disappearance of psychological distress does no always occur upon proper endocrine treatment (129,130). These persisting physical and psychological impairments may affect quality of life in patients with Cushing’s disease despite long-term biochemical cure. However, the long-term impact of Cushing’s disease on subjective well-being after successful treatment of cortisol excess is unclear.

SCOPE OF THIS THESIS

In this thesis, severel aspects of Cushing’s syndrome will be adressed, including characterization of temporal changes in hormonal secretion, diagnosis of Cushing’s syndrome, transsphenoidal surgery and complications, postoperative evaluation and follow-up.

Characterization of temporal changes in hormonal secretion

ACTH-independent Cushing’s syndrome is caused by excessive secretion of cortisol by an adrenocortical adenoma or carcinoma, or, rarely, micro-or macronodular bilateral adrenal hyperplasia. We investigated whether the differences between these adrenal causes of Cushing’s syndrome might also be reflected in the temporal architecture of cortisol concentrations. Therefore, in chapter 2, the secretory profiles
of cortisol in primary adrenal Cushing’s syndrome are described. Quantitative data were analyzed of basal and pulsatile secretion, diurnal rhythmicity and secretory process regularity, comparing unilateral adenoma and bilateral macronodular hyperplasia. Moreover, neurosecretory control of tumoral cortisol secretion in primary adrenal hypercortisolism was compared with that in pituitary dependent Cushing’s disease.

In pituitary-dependent hypercortisolism, the diminished growth hormone (GH) response to various stimuli, including GHRH, insulin-induced hypoglycaemia and ghrelin, is well-known. In addition, GH secretion was negatively correlated to 24 hr urinary cortisol excretion and the GH secretorion regularity was significantly decreased. These GH secretory abnormalities could be the result of the presence of the pituitary adenoma itself, a tumoral product acting as a paracrine signal on the somatotrope or the result of cortisol excess per se. In order to further explore these observations, in chapter 3, the dynamics of spontaneous GH secretion in patients with primary adrenal Cushing’s syndrome are described, since these patients lack a pituitary adenoma, but otherwise suffer from chronic endogenous cortisol excess. The prime question was whether such patients display low-amplitude and/or disorderly GH secretion compared with BMI-matched controls, as we previously found in pituitary-dependent hypercortisolism.

When transsphenoidal surgery fails to induce remission of Cushing’s disease, bilateral adrenalectomy can be performed. However, this harbours the risk of developing Nelson’s syndrome, characterized by grossly elevated ACTH concentrations, a sellar mass and skin hyperpigmentation. In chapter 4, the issue is addressed whether the mechanisms directing ACTH secretion differ in Nelson’s syndrome and untreated Cushing’s disease, by analyzing 24 h ACTH profiles in these distinct conditions.

**Diagnosis of Cushing’s syndrome**

In the case of clinical suspicion of Cushing’s syndrome, biochemical screening for hypercortisolism is performed. Twenty-four hour urine collection for the measurement of urinary free cortisol excretion and the low-dose dexamethasone suppression test (1 mg) have been used extensively as first line screenings tests for CS, but neither test has proven fully capable of distinguishing all cases of CS from other individuals. Since several years, measuring late night salivary cortisol concentration has emerged as a screening test for the presence of hypercortisolism. Despite its simplicity, the use of salivary cortisol measurement to screen for Cushing’s syndrome has been slow to catch on. In chapter 5, several aspects of salivary cortisol measurement in the diagnosis of Cushing’s syndrome are discussed. Physiology of cortisol in saliva, collection methods, technical aspects of measuring salivary cortisol concentration, especially the validation of an automated assay on the Roche immunoanalyzer, confounding factors and establishment of reference ranges are described. Furthermore, published data on the clinical use of late-night salivary cortisol measurement in the diagnosis of Cushing’s syndrome are discussed.
Treatment of Cushing’s disease: transsphenoidal surgery and complications

Transsphenoidal surgery (TSS) is the treatment of choice for most lesions in the sellar region, including pituitary-dependent Cushing’s disease. Meningitis still occurs as a complication of TSS, with its incidence ranging from 0.4% to 9%. In chapter 6, possible risk factors for meningitis after transsphenoidal surgery are addressed. We also studied the value of preoperative nasal cultures in relation to the pathogens isolated from the cerebrospinal fluid (CSF).

Meningitis after TSS is considered to occur by infection via a CSF fistula in the postoperative period. Therefore, when intraoperative CSF leakage is observed, meticulous, watertight reconstruction of the sellar floor should be performed, in order to prevent the formation of a CSF fistula. In addition, an external lumbar drain (ELD) can be inserted to prevent postoperative rhinorrhea and fistula formation. However, the effect of ELD insertion on the risk of postoperative meningitis, has not been described yet. In chapter 7, the question is addressed whether routine postoperative external cerebro-spinal fluid (CSF) drainage in case of intraoperative CSF-leakage, can reduce the risk of postoperative meningitis.

Postoperative evaluation and long term follow-up after transsphenoidal surgery for Cushing’s disease

Following transsphenoidal surgery for pituitary-dependent Cushing’s disease, usually an extensive biochemical evaluation is employed in order to establish remission of disease and future prognosis. Chapter 8 provides data on the use of a postoperative metyrapone test in the early assessment of outcome of pituitary surgery for Cushing’s disease.

In chapter 9, the outcome of transsphenoidal surgery and the long-term predictive value of postsurgical cortisol concentrations is described in establishing cure and risk of recurrence in Cushing’s disease in patients treated by transsphenoidal surgery.

With a few exceptions, most studies on the success of treatment of Cushing’s disease have focussed on hard biochemical outcome rather than functional recovery. Therefore, in chapter 10, we evaluated various physical and psychological aspects of quality of life in cured patients with Cushing’s disease, using four validated health-related quality of life questionnaires and comparing the results with a control group with equal age and sex distribution and with literature reference ranges.

Finally, chapter 11 provides the summary and conclusions from this thesis.
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