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Cushing's Syndrome : hormonal secretion patterns, treatment and outcome.

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Chapter 11
Summary and Conclusions

Endogenous Cushing's syndrome is a clinical state resulting from prolonged, inappropriate exposure to excessive secretion of cortisol. 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. Biochemically, Cushing's syndrome is characterized by loss of normal feedback regulation of the hypothalamo-pituitary-adrenal (HPA)-axis and of the normal circadian rhythm of cortisol secretion. The etiology of Cushing's syndrome can be divided in ACTH-dependent and ACTH-independent causes. 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.

The diagnosis, treatment and follow-up of patients with Cushing's syndrome remains a challenge to clinicians. In this thesis, several aspects of Cushing's syndrome are addressed, 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 successful treatment of Cushing's disease.

CHARACTERIZATION OF TEMPORAL CHANGES IN HORMONAL SECRETION

Cortisol Secretion in Primary Adrenal Cushing's Syndrome

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. Furthermore, the cortisol-secretion pattern showed more disorderliness compared to healthy controls. It was unclear to which extent the cortisol secretory patterns are different among the different causes of Cushing's syndrome. Therefore, we wondered whether the differences between pituitary and adrenal causes of Cushing's syndrome might also be reflected in an altered temporal architecture of cortisol concentrations. Therefore, in **chapter 2**, the secretory profiles of cortisol in primary adrenal Cushing's syndrome are described. Twelve patients with primary adrenal Cushing's disease (7 with a unilateral adenoma and 5 with bilateral macronodular hyperplasia), 12 patients with pituitary-dependent hypercortisolism and 12 age- and gender matched controls were studied. 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 patients with primary adrenal Cushing's syndrome, basal cortisol secretion was increased two-fold and pulsatile secretion was also increased two-fold, attributable to increased pulse frequency. All patients with primary adrenal Cushing's syndrome showed a significant diurnal rhythm with a delay phase shift of 3h. Approximate entropy ratio was increased compared to controls, denoting loss of autoregulation. Comparing unilateral adrenal versus bilateral macronodular disease (AIMAH) revealed a slightly decreased burst mass in AIMAH and a 2-fold increase in cosinor amplitude in unilateral adenoma's. No significant differences were found in cortisol profiles between pituitary-dependent Cushing's disease and primary adrenal hypercortisolism, except from a normal acrophase timing in pituitary-dependent Cushing's disease. Apparently, the adrenal gland reacts in a stereotypic pattern, irrespective of the pathophysiological mechanism of cortisol excess. The partial preservation of secretory regularity and diurnal rhythmicity in patients with primary adrenal Cushing's syndrome point to incomplete autonomy of these tumors. Several intra- or extra-adrenal factors might contribute to this (modified) diurnal cortisol rhythm in the absence of the physiological ACTH oscillator. Possible regulatory signals are the effect of non-ACTH hormones and their respective receptors expressed in the adrenal tumors, paracrine actions of neuropeptides, increased leptin concentrations, interactions between adrenal cortex and medulla, or splanchnic neuronal input on the adrenal glands.

These findings challenge the view that cortisol secretion in primary adrenal Cushing's syndrome is a purely autonomous process. The role of other regulatory signals than ACTH in the (patho-)physiology of adrenal cortisol secretion is an interesting field of further investigation. The identification and exploration of these regulatory factors might lead to new therapeutic options for the control of hypercortisolism in patients with ACTH-independent Cushing's syndrome. This has already been shown for patients with Cushing's syndrome due to bilateral macronodular adrenal hyperplasia, with LH-dependent hypercortisolism. In these patients, from which one patient at our institution, the administration of Leuprorelide, an LHRH-agonist, resulted in complete normalisation of cortisol secretion. Also, one patient has been reported with catecholamine-dependent hypercortisolism, which was successfully treated by the administration of propranolol.

GH Secretion in Primary Adrenal Cushing's Syndrome

In adult patients, sustained hypercortisolism is known to have adverse catabolic effects on various tissues, leading to muscle atrophy and osteoporosis. Concomitantly,

GH responses to various stimuli, including insulin-induced hypoglycemia, GHRH, growth hormone secretagogues and ghrelin are diminished. In a previous study in patients with pituitary-dependent hypercortisolism the 24 h GH secretion was negatively correlated to urinary cortisol excretion and the GH secretion regularity was significantly decreased. Hypothetically, 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 somatotrops or the result of cortisol excess per se on the somatotrophic axis.

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, like we previously found in pituitary-dependent hypercortisolism.

We investigated spontaneous 24 h GH secretion in adult patients with ACTH-independent hypercortisolism. Seven patients had a unilateral cortisol-producing adenoma and 5 others bilateral nodular hyperplasia. Plasma GH concentration profiles (10 min samples) were analyzed by deconvolution to reconstruct secretion and approximate entropy to quantitate orderliness of the release process. Comparisons were made with a BMI-, age- and gender-matched control group and an age- and gender-matched group of lean controls.

In patients with primary adrenal Cushing's syndrome, GH secretion rates did not differ from BMI-matched controls, but was 50 % reduced compared to lean controls, caused by 2.5-fold decrease in burst mass at similar pulse frequency. Approximate entropy was increased in patients compared with both control groups, denoting more irregular GH secretion patterns. Total serum IGF-I concentrations were similar in the 3 groups. The temporal changes of GH secretion in primary adrenal Cushing's syndrome are in line with the previously reported data on GH secretion in pituitary Cushing's disease. Therefore, in pituitary Cushing's disease, the presence of the pituitary adenoma itself or a tumoral product acting as a paracrine signal do not seem to play a role in changing the dynamics of GH secretion. We could not find a relation between the degree of cortisol excess and GH secretion rate, as we previously found for pituitary-dependent hypercortisolism. A conspicuous difference in clinical presentation between the two forms of the syndrome was the very high cortisol secretion rate in some of the (male) pituitary-dependent Cushing's disease patients, which could explain the divergent results.

We conclude that hyposomatotropism in Cushing's syndrome is only partly explained (~30%) by increased body weight, and that increased GH secretory irregularity suggests altered coordinated regulation of GH release. In the absence of a significant change in basal (non-pulsatile) secretion this observation is compatible with increased somatostatin inhibition, decreased hypothalamic GHRH secretion, a defect in the GHRH/GH secretagogue receptor signalling or direct non-receptor-related GH inhibition. Other mechanisms might limit GH secretion in chronic hypercortisolism, including decreased mitosis and increased apoptosis of pituitary cells, the inhibitory effect of glucocorticoids on GH secretion *via* the action of annexin 1, or the influence of leptin on GH secretion. In view of the unchanged IGF-I feedback signal in the patients, decreased regularity of GH secretion could reflect impaired coordinated control of GH secretion by somatostatin, GHRH and ghrelin and/or altered pituitary responsiveness to these peptides. The present

data do not address the reversibility of disorderly GH release due to endogenous adrenal cortisol excess with presumably normal premorbid hypothalamo-pituitary function. Studying the 24 h GH secretion in the same patient group with primary adrenal Cushing's syndrome, after long-term correction of hypercortisolism by (bilateral) adrenalectomy could further clarify the (ir)reversibility of the effects of chronic glucocorticoid excess on the somatotrophic axis.

Nelson's syndrome

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). Cushing's disease and Nelson's syndrome are considered to be distinct pathoetiological presentations of the same primary biological entity. 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.

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.

Basal ACTH secretion was increased 6-fold and pulsatile secretion 9-fold in patients with Nelson's syndrome compared with Cushing's disease. The increase in pulsatile secretion was due to an 8-fold augmentation of burst mass. Event frequency was comparable between both patient groups and higher than in normal controls. Paradoxically, the consistency of subordinate patterns of serial ACTH release, albeit disrupted in active Cushing's disease, was normal in Nelson's syndrome. Normal ACTH secretory-process regularity in Nelson's syndrome was attributable to a more reproducible (lower ApEn) succession of ACTH secretory-burst mass denoting more uniform amplitude evolution over 24 h. On the other hand, the quantifiable regularity of serial interburst intervals (waiting times) was unexpectedly elevated in Nelson's syndrome. Nelson patients maintained a significant diurnal rhythm in ACTH release, which was marked by a 15-fold greater amplitude and a 4-h acrophase (maximum) delay. The present detailed analyses delineate marked ACTH secretory-burst mass amplification and (amplitude-independent) anomalous regularity of successive pulse size and timing in Nelson's syndrome compared with Cushing's disease or controls. We postulate that the foregoing novel distinctions are due to unique tumoral secretory properties, concurrently required glucocorticoid replacement and/or hypothalamic injury associated with prior radiotherapy in Nelson's syndrome.

DIAGNOSIS OF CUSHING'S SYNDROME: LATE-NIGHT SALIVARY CORTISOL

It can be very 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 cortisol excess, even a low index of suspicion should mandate at least a screening evaluation for Cushing's syndrome.

There are several diagnostic tools available for the biochemical screening for hypercortisolism.

Twenty-four hour urine collection for the measurement of urinary free cortisol (UFC) has been considered a gold standard for the diagnosis of CS. However, urinary cortisol excretion may be normal in patients with subclinical CS in whom hypercortisolism is still mild. In addition, mild elevations of urinary cortisol can also be found in pseudo-Cushing's states and pregnant women, and some medications, such as carbamazepin and digoxin, can give false elevations of UFC. The low-dose dexamethasone suppression test (DST) is the second screening test. The low-dose DST consists of the oral intake of 1 mg dexamethasone between 2300 and 2400 h, and measurement of fasting plasma cortisol concentration between 0800 and 0900 h the following morning. This test has also several limitations, including low specificity when a low cut-off level (below 50 nmol/l) is used, interference of drugs, and interperson variability of cortisol-suppression after low dose dexamethasone. Furthermore, in some patients with Cushing's syndrome, serum cortisol concentrations below 54 nmol/l after 1 mg dexamethasone have been found.

The third screening test for hypercortisolism is measurement of midnight serum cortisol concentration. In two studies, a single midnight serum cortisol value correctly identified almost all subjects with Cushing's syndrome. 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, recently introduced screening test is the measurement of cortisol concentrations in saliva. Salivary cortisol is a valid indicator of the plasma free cortisol concentration, and independent of changes in cortisol binding globulin (CBG) concentration and the rate of saliva production. The concentration of cortisol in saliva is about 5% of the total plasma cortisol concentration. In **chapter 5**, several aspects of salivary cortisol measurement in the diagnosis of Cushing's syndrome are discussed.

A sample of saliva can easily be collected at home, using a special device, a Salivette (Sarstedt), stored at room temperature for at least a week and transferred to the laboratory by regular post without influencing the salivary cortisol concentration.

We validated an automated assay for salivary cortisol measurement on the Roche immunoanalyzer, with a functional detection limit of 2 nmol/l, and adequate reproducibility in the low nanomolar range. Possible confounding factors are contamination of the saliva sample with traces of blood, substances interfering with 11 β -Hydroxysteroid dehydrogenase type II and the use of exogenous steroids, including inhalers and topic agents. Reference ranges are dependent on the assay method and should be established in each laboratory.

Several clinical studies have been performed using salivary cortisol as a first line test in screening for CS. In all studies, late-night salivary cortisol-concentration performed well in establishing hypercortisolism, with sensitivity and specificity ranging from 92 to 100%. However, these studies have mostly been performed in a research setting, with in-patients, under ideal conditions to accomplish the desired outcome. Also, 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, at least partly explained by the use of different assays.

In conclusion, measurement of salivary cortisol concentration using new, sensitive and, recently, automated assay techniques is reliable and simple, making it a suitable test for daily clinical practice. Late-night salivary cortisol measurement will have to prove itself in daily clinical practice as a reliable test for screening for Cushing's syndrome. Careful clinical evaluation and, when Cushing's syndrome is suspected, the combination of at least two screening tests is the current guideline to diagnose Cushing's syndrome. The diagnostic evaluation to establish the precise etiology of hypercortisolism should not proceed unless the diagnosis of Cushing's syndrome is unequivocal. Measurement of salivary cortisol concentration might also be useful in the evaluation and individual optimisation of glucocorticoid suppletion in patients with adrenal insufficiency, in patients using ortho-para DDD, and as a research tool for the assessment of the Hypothalamic-Pituitary-Adrenal axis in other (patho)-physiological states, including critically ill patients.

TREATMENT OF CUSHING'S DISEASE: TRANSSPHENOIDAL SURGERY AND COMPLICATIONS

Risk factors for meningitis after transsphenoidal surgery

Transsphenoidal surgery (TSS) is the treatment of choice for most lesions in the sellar region, including pituitary-dependent Cushing's disease. In the literature, the incidence of postoperative meningitis after transsphenoidal surgery ranges from 0.4% to 9%, with an overrepresentation of patients with Cushing's disease. In **chapter 6**, we retrospectively reviewed the results of 228 consecutive transsphenoidal operations in which a standard regimen of amoxicillin prophylaxis was used to evaluate possible risk factors for meningitis. We also studied the value of preoperative nasal cultures in relation to the pathogens isolated from the cerebrospinal fluid (CSF).

The incidence of meningitis was 3.1% (seven of 228 cases). Four out of seven patients had been operated for Cushing's disease. Postoperative CSF leakage was shown to be an important risk factor of meningitis after transsphenoidal surgery (six of seven patients with postoperative CSF rhinorrhea and only one of 221 patients without postoperative CSF rhinorrhea developed meningitis). Cultures of preoperative specimens from the anterior nasal vestibule did not have any predictive value in our study. Therefore, we do not advocate routine culturing of preoperative nasal swab specimens before TSS. Since two of our three patients with radiological signs of sinusitis developed meningitis, we would recommend the inclusion of routine radiological imaging of the paranasal sinuses in the preoperative workup for TSS. Sinusitis should be treated adequately, and TSS should be postponed for at least 4 weeks. Prospective studies are needed to determine preoperative prophylaxis for patients undergoing TSS, especially those with postoperative CSF leakage.

Postoperative external lumbar drainage and the risk for meningitis

During transsphenoidal surgery, cerebrospinal fluid (CSF) leakage can occur, especially in cases with suprasellar extending pituitary tumors. The management of intraoperative CSF leakage during transsphenoidal surgery 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. Previously, as described in chapter 5 of this thesis, we identified postoperative CSF leakage as a risk factor for meningitis after transsphenoidal surgery. However, the effect of ELD insertion on the risk of postoperative meningitis, had not been described yet.

In chapter 7, the question is addressed whether routine postoperative external CSF drainage in case of intraoperative CSF-leakage, can reduce the risk of postoperative meningitis.

We retrospectively reviewed a series of 278 consecutive transsphenoidal operations. In all operations with intraoperative CSF leakage, an external lumbar ELD was inserted directly postoperatively, and removed after at least 5 days.

The incidence of postoperative meningitis was compared with that in a previously studied series of 228 consecutive transsphenoidal operations, without insertion of an ELD in cases with intraoperative CSF leakage.

In the present series, postoperative meningitis occurred in 2/278 (0.7%) operations, compared to 7/228 (3.1%) operations in the previous study period ($P < 0.05$). Intraoperative CSF leakage was noted in 70/278 (25.2%) operations. All these patients received an ELD immediately after surgery for at least 5 days. There were no reported complications of ELD insertion. In the present series, 1 of 70 (1.4%) patients with intraoperative CSF leakage developed meningitis, compared to 3 of 22 (13.6%) patients in the previous study ($P < 0.05$).

The present study suggests that the routine insertion of an ELD in patients in whom intraoperative CSF leakage is observed, considerably reduces the incidence

of postoperative meningitis. The incidence of only 0.7% post-TSS meningitis compares favourably with the 3.1% in our previous study and also with the reported incidence of 0.4 - 9% in other series. Furthermore, there were no reported complications of ELD insertion and no drain-related infections. Recent studies have shown that for small CSF leaks, adequate local repair of the defect may obviate the need for lumbar drain placement, both in conventional transsphenoidal surgery as in endoscopic transsphenoidal surgical procedures. Therefore, insertion of a lumbar drain might be reserved for patients with a large dural defect or patients in whom the dural repair is not completely watertight. This more restrictive approach in the use of postoperative lumbar drainage after transsphenoidal surgery is probably safe, without increasing the incidence of postoperative meningitis. Moreover, this approach is more patient-friendly, obviating postoperative bed rest. This is especially important for patients treated for Cushing's disease, who are at an increased risk of arterial and venous thrombosis.

POSTOPERATIVE EVALUATION AND FOLLOW-UP

Although transsphenoidal surgery allows cure of Cushing's disease, the reported success rates vary from 50 to almost 90%. Immediate postoperative assessment of outcome of pituitary surgery is important in order to plan further treatment in patients with persistent hypercortisolism. Early postoperative assessment is also valuable as an early marker of the risk of relapse of Cushing's syndrome. For the assessment of cure and risk of relapse after pituitary surgery for Cushing's disease, several tests have been used. We evaluated two of these methods.

Postoperative metyrapone test

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. Metyrapone is a potent inhibitor of 11- β -hydroxylase, an enzyme involved in the last step of adrenal cortisol synthesis, converting 11-deoxycortisol to cortisol. Under normal circumstances, administration of metyrapone results in lowering of the serum cortisol-concentration followed by an increase in pituitary ACTH-release and subsequent rise in 11-deoxycortisol.

A metyrapone test was performed 14 days postoperatively in 29 patients who had been treated for Cushing's disease by transsphenoidal surgery. Twelve patients were not in remission after surgery. These patients all had 11-deoxycortisol levels > 350 nmol/l. Seventeen patients met the criteria for early remission, defined as a fasting serum cortisol less than 140 nmol/l and/or a 24-hour urinary cortisol excretion less than 250 nmol/l. Four of these patients had serum 11-deoxycortisol levels between 150 nmol/l and 350 nmol/l after metyrapone. Three of these 4 patients experienced a relapse of Cushing's disease during follow-up, after 17, 32 and 80 months. In

the 13 patients with a serum 11-deoxycortisol <150 nmol/l after metyrapone, no relapse occurred during a median follow-up of 35 months.

From this retrospective series it was concluded that the metyrapone test is a useful test in the assessment of outcome of pituitary surgery for Cushing's disease, with a sensitivity of 100% and a specificity of 75% for the early detection of patients at risk of a relapse.

Although these results are promising, it is a retrospective study in a limited number of patients and a relative short median follow-up of 35 months. The preoperative use of cortisol-lowering drugs such as ketoconazole and the peri-operative glucocorticoid regime might also influence the results of early postoperative tests, and these factors should also be taken into account. Prospective, large studies with long-term follow-up are needed in order to determine the optimal assessment of cure and risk of recurrence in patients treated for Cushing's disease.

Long-term predictive value of postsurgical cortisol concentrations

In **chapter 9**, 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 (TS).

TS initially cured 56 (72%) of 78 patients with Cushing's disease. During a median follow-up of 7 years, 5 (9%) patients had recurrent Cushing's disease. In patients with a follow-up of more than 10 years, recurrence occurred in 4 (17%) of 24 patients. Considering the risk of recurrent disease, all patients with Cushing's disease cured by transsphenoidal surgery require long-term follow-up.

In addition, we found that a low postoperative plasma cortisol level (i.e. below 138 nmol/L), irrespective whether determined 2 weeks or 3 months postoperatively, is a good predictor of cure of the disease. However, the present study also indicates that plasma cortisol levels above 138 nmol/L, obtained two weeks after TS, can not be used indiscriminately to predict persistent Cushing's disease, as 8 (27%) out of 30 patients with cortisol > 138 nmol/L were cured when patients were evaluated at 3 months postoperatively. In these 8 patients, repeat immediate surgery for persistent postoperative Cushing's disease would have been inappropriate, because they were cured despite detectable postoperative cortisol levels. Finally, the current study proves that postoperative cortisol levels do not positively predict recurrence of disease during long-term follow-up of initially cured patients.

QUALITY OF LIFE AFTER SUCCESSFUL TREATMENT OF CUSHING'S DISEASE

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.

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.

In **chapter 10** we assessed quality of life in patients with Cushing's disease treated in our center by transsphenoidal surgery, and, if necessary, by additional treatment consisting of pituitary irradiation and/or bilateral adrenalectomy. We used four validated health-related quality of life questionnaires and compared the results with a healthy control group with equal age and sex distribution and with literature reference ranges. The purpose of the study was to evaluate various physical and psychological aspects of quality of life in cured patients with Cushing's disease.

General perceived well-being as measured by the Nottingham Health Profile (NHP) and the Short Form (SF-36) was reduced compared with controls for all subscales. Patients with Cushing's disease also had lower scores on fatigue (Multidimensional Fatigue Index: MFI-20), anxiety and depression (Hospital Anxiety and Depression Scale: HADS). Compared with age-adjusted mean reference values available from the literature, quality of life was also reduced in patients treated for Cushing's disease according to all questionnaires and all items, except pain (SF-36), sleep (NHP) and reduced activity (MFI-20).

Hypopituitarism after treatment for Cushing's disease was associated with decreased quality of life on physical, fatigue and depression scales. Independent predictors of quality of life were age (physical subscales), gender (fatigue subscales) and hypopituitarism (physical and fatigue subscales).

The present data indicate that despite long term biochemical cure Cushing's disease induces persistent, most likely irreversible, limitations in both physical and mental functioning, thereby reducing quality of life. Several mechanism may explain this observation. The impaired quality of life after long-term remission of Cushing's disease may be related to irreversible, glucocorticoid-induced changes in the central nervous system. It has been demonstrated in rodents, that cortisol excess results in irreversible changes in the central nervous system. In the hypothalamus, cortisol excess has profound effects on the plasticity of neurons. Therefore, we postulate that irreversible changes may be present in patients cured for Cushing's disease. The finding of reduced quality of life in patients with hypopituitarism might also be explained by intrinsic shortcomings of hormone replacement therapy. In the present study, patients with hypopituitarism did not receive DHEA-suppletion, which has been shown to improve quality of life scores in women with adrenal insufficiency. Long-term endocrine withdrawal effects following correction of longstanding hypercortisolism might also explain in part the reduced quality of life scores.

In our cohort, 26 (45%) patients had a total HADS-score larger than 13, indicating depression. This can explain our finding of a significant association between the anxiety and depression scores as assessed with the HADS and all other quality of life scores, and reflects the important influence of depression and anxiety symptoms on the experience of all other complaints.

The present study documents the discrepancy between the notion of doctors of cure of Cushing's disease versus the persistence of complaints in patients. Moreover, the manifestations of reduced quality of life can not readily assessed by clinical or biochemical assessment, which may complicate doctor-patient relationships. Further research on optimal management of patients after correction of hypercortisolism is warranted, including optimisation of hormone replacement therapy and treatment of coexistent psychological symptoms.