Cushing’s syndrome – A structured short- and long-term management plan for patients in remission

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Abstract

One-hundred years have passed since Harvey Williams Cushing presented the first patient with the syndrome that bears his name. In patients with Cushing’s syndrome body composition, lipid-, carbohydrate- and protein-metabolism is dramatically affected and psychopathology and cognitive dysfunction is frequently observed. Untreated patients with Cushing’s syndrome have a grave prognosis with an estimated five-year survival of only 50%. Remission can be achieved by surgery, radiotherapy and sometimes with medical therapy. Recent data indicate that the adverse metabolic consequences of Cushing’s syndrome are present for years after successful treatment. In addition, recent studies have demonstrated that health related quality of life and cognitive function is impaired in patients with Cushing’s syndrome in long-term remission. The focus of specialized care should therefore not only be on the diagnostic work-up and the early post-operative management, but also the long-term follow-up. In this paper we review the long-term consequences in patients with Cushing’s syndrome in remission with focus on the neuropsychological effects and discuss the importance of these findings for long-term management. We also discuss three different phases in the postoperative management of surgically treated patients with Cushing’s syndrome, each phase distinguished by specific challenges; the immediate post-operative phase, the glucocorticoid dose tapering phase and the long-term management. The focus of the long-term specialized care should be to identify cognitive impairments and psychiatric disorders, evaluate cardiovascular risk, follow pituitary function and to detect possible recurrence of Cushing’s syndrome.
Introduction

“Physical examination showed an undersized, kyphotic young woman of most extraordinary appearance. Her round face was dusky and cyanosed and there was an abnormal growth of hair. Her abdominal body had the appearance of a full-term pregnancy.”

One-hundred years have passed since Harvey Williams Cushing presented the first patient with the syndrome that bears his name. The patient was a 23-year-old woman with "the most peculiar appearance". Her abdomen was huge and the face large and round with hypertrichosis and hyperpigmentation. She had gained weight and suffered from muscle weakness, back pain, irregular menstruation and elevated blood pressure. More than 20 years later Cushing reported on additional 11 patients. Besides having similar clinical features he also noted at autopsy that some of these patients had a small pituitary basophilic adenoma. Ten years later Fuller Albright stated that this clinical picture was caused by “hyperadrenocorticism” with excess production of a “sugar-hormone”, today called glucocorticoids (GCs). He declared that the clinical state, irrespective of aetiology, should be called Cushing’s syndrome (CS) and when caused by pituitary adenoma it should be called Cushing’s disease (CD).

Aetiology

CS is a clinical state caused by chronic overexposure of GCs. The typical features of CS are weight gain, central obesity, muscle and skin atrophy, osteoporosis, hypertension, impaired glucose tolerance, dyslipidemia, fatigue, depression and cognitive impairment. The most common cause of CS is iatrogenic, i.e. caused by pharmacological GC treatment (exogenous CS). Endogenous CS is an uncommon condition with an incidence between 1.8-2.4 patients per million/year. This incidence rate is mainly based on two studies, a nationwide Danish
survey\textsuperscript{6} and a study from New Zealand\textsuperscript{7}, supported by two other smaller studies\textsuperscript{8,9}. The median age at diagnosis is 40 years with a female to male ratio of 3:1\textsuperscript{6,7}. The most common cause of endogenous CS is CD (ACTH producing pituitary adenoma), seen in approximately 70\% of patients with CS. Cortisol producing adrenal adenoma and ectopic ACTH producing tumours are less common, each accounting for approximately 10-15\% of cases.

**Treatment**

The first line treatment for patients with CD is transsphenoidal pituitary surgery (TSS) and unilateral adrenalectomy for cortisol producing adrenal adenoma\textsuperscript{10}. Unilateral adrenalectomy is curative in almost all patients with cortisol producing adrenal adenoma and permanent adrenal insufficiency is rare. Conversely, hypopituitarism is common after TSS, with a range between 13 and 81\%\textsuperscript{11-15}. Most common is gonadal axis dysfunction and growth hormone (GH) deficiency while central hypothyroidism and diabetes insipidus are less frequently observed\textsuperscript{15-17}. Determining factors for the development of hypopituitarism are the size of the tumour (microadenoma versus macroadenoma), the surgical approach (adenomectomy versus hypophysectomy) and the experience of the surgeon, \textit{i.e.}, patients with microadenomas that are operated by an experienced neurosurgeon with selective adenomectomy have the lowest risk of hypopituitarism\textsuperscript{11,15}. Furthermore, 14-29\% of patients with CD are not cured after TSS, and additionally 9-25\% of patients relapse at long-term follow-up after an initially successful treatment\textsuperscript{15,18,19}. In a study on 184 patients with ACTH producing microadenoma who achieved remission after transsphenoidal surgery, 0.5, 11 and 26\% of the patients relapsed after 1, 3 and 5 years, respectively\textsuperscript{18}. Second-line treatments, such as additional neurosurgical intervention, radiation therapy and/or bilateral adrenalectomy, may then become necessary which further increases the risk for impaired pituitary function and compromised long-term outcome\textsuperscript{20}.
Outcome

Mortality

“The average duration of the disease from onset to death is slightly over five years.”

Untreated patients with CS have a grave prognosis with an estimated 5 year survival of only 50%2, 21. Even in patients who have received treatment for CS mortality increased, both in comparison to the normal population6-8, 22, 23 and to patients with non-functioning pituitary adenomas24. However, achievement of remission is of fundamental importance since patients who are not cured have much worse prognosis than patients in remission6. In a recent paper on 343 patients with CS, mortality rate was higher than in the normal populatin23. The greatest mortality risk was observed during the first year after treatment. However, the mortality risk at long-term follow-up was also significantly increase, hazard ratio being twice as high when compared to the control group23. No difference in mortality rate was seen between patients treated for CD or cortisol producing adrenal adenoma.

Cardiovascular risk

“The heart was enlarged and the aorta atheromatous.”

Patients with active CS have adverse cardiovascular risk profile25, and the majority have central obesity, hypertension, dyslipidemia and impaired glucose tolerance or diabetes mellitus26. Echocardiographically, active CS is characterized by left ventricular hypertrophy, diastolic and systolic dysfunction27, 28 that are at least partially explained by increased myocardial fibrosis29. Although significant improvement is reported after cure, especially after treatment for cortisol producing adrenal adenoma26, a substantial number of patients still have an adverse cardiovascular risk profile30. Indeed, 27% of patients treated for CD have atherosclerotic plaques at 5 years of follow-up, compared with only 3% of gender, age and
BMImatched controls. Conversely, left ventricular structure and function seem to be restored following treatment.

Coronary artery disease is more prevalent in patients with CS in remission compared with healthy individuals, especially women and younger patients. In another recently published population-based cohort study, increased risk for acute myocardial infarction, congestive heart failure, stroke and venous thromboembolism during the first year after treatment for CS, in comparison to the normal population, was observed. In the same study, the risk for acute myocardial infarction at long-term follow-up was nearly 4-times greater in the patients treated for CS. In agreement with the echocardiographic studies, the risk for congestive heart failure seems not to be increased at long-term follow-up.

Bone

“A marked osteoporosis of the skeleton was found, it being easily possible to cut the vertebral bodies with a knife, the spongy part of the bone having largely disappeared.”

Decreased bone mineral density (BMD), osteoporosis and osteoporotic fractures are important features of endogenous CS. In patients with CS in remission, longer duration of postoperative GC replacement therapy and duration of active disease are both associated with low BMD. Prospective studies have demonstrated improved BMD following treatment of CS. These studies are however limited by low number of patients, short follow-up time and/or lack of a control group. Two studies performed at long-time follow-up have presented conflicting results. In a prospective study on 18 patients with CS in remission from Norway, BMD Z-scores at all sites were normalized after 6 years, while in a cross-sectional study from Spain, 37 women with CS in remission for a mean time of 6 years had decreased BMD compared to matched controls.

Quality of life, psychopathology and cognitive function
“He found himself without energy, easily fatigued, unable to concentrate his mind on his work, and fits of unnatural irritability alternated with periods of depression.”

**Patients with active Cushing’s syndrome**

Patients with active CS have markedly impaired quality of life (QoL), both in comparison to healthy individuals and patients with other pituitary tumours. Patients with active CS also have substantial psychiatric problems. Up to 80% have generalized anxiety and 70% have major depression. Although not as common, manic or hypomanic symptoms may occur and be among the early manifestations of the disease.

Cognitive function is also negatively affected in patients with CS. In an early study on 35 patients with active CS, diffuse bilateral cerebral dysfunction was found in two-thirds of patients. Nonverbal visual-ideational and visual memory functions were most severely affected. In another study on 23 patients with CS, 66% had difficulty in concentration and 83% had memory impairments.

Morphological changes in the central nervous system are also reported in patients with active CS, including decreased total brain volume and hippocampal volume, compared with healthy subjects. A significant correlation has been found between the degree of hypercortisolism, the extent of cognitive impairment and decreased hippocampal volume.

**Patients with Cushing’s syndrome in remission**

After treatment, QoL improves, but is still worse than in controls (figure 1). Furthermore, fatigue, which is one of the most common and distressing symptoms in patients with CS, has been reported by 41-85% of patients at long term follow-up after treatment. In prospective studies, psychiatric abnormalities are reported to improve after treatment. In one study, 33 patients with CS were examined by structured interviews as well as...
questionnaires before and at 3, 6 and 12 months after correction of hypercortisolism. Before treatment, two-thirds had significant psychopathology that was predominantly in the form of atypical depressive disorder. After remission, overall psychopathology decreased significantly to 54% at 3 months, 36% at 6 months and 24% at 12 months. Even at long-term follow-up, patients with a mean duration of remission of 11 years showed an increased prevalence of apathy, irritability, anxiety and depression.

Improvements in cognitive function and morphological brain changes occur following treatment. However, the number of patients in these studies was limited (between 13-33 patients) and the follow-up times were short (1-2 years) (table 1). Recently, cognitive function at long-term follow-up in patients with CS in remission has been addressed. In a study from the Netherlands, cognitive function in 74 patients with CD in remission was compared to 74 healthy individuals and 54 patients previously treated for a non-functioning pituitary adenoma. The mean ± SD duration of remission was 13 ± 13 years (range 1 and 51 years). The cognitive testing was mainly focused on memory and executive functioning and showed worse performance in patients with CD compared with both control groups. Even global cognitive functioning, evaluated using the Mini Mental State Examination, was significantly worse in the CD patients. In another recent study, memory, hippocampal and brain grey matter volume were evaluated in 11 patients with active CS, 22 patients with CS in remission (mean ± SD time of biochemical control 7.3 years ± 2.4) and 34 matched controls. No difference in cognitive function or brain volumes were seen between patients with active CS or patients in remission wherefore the groups were pooled together in the analysis. In patients with CS verbal and visual memory were found to be impaired compared with controls. Interestingly, brain gray matter volumes, evaluated using MRI, were decreased in patients with CS, although no significant difference in hippocampal volume was seen. In children with CS, a decline in cognitive function has been reported following cure.
study on 11 children with CS, 8-16 years old, no difference in IQ or psychopathology was seen before treatment when compared to controls, although smaller cerebral volumes, larger ventricles and smaller amygdale was documented. One year after treatment, despite reversal of cerebral atrophy, a decline in IQ and school performance was observed. This is in a disagreement with findings in adults. Self-perceived health related QoL in paediatric CS patients has also been shown to be impaired. One year postoperatively improvement is seen, though residual impairment remains.

We have recently demonstrated that various domains of cognitive function are compromised in patients with CS after long-term remission. In a cross-sectional study, cognitive function in 43 patients previously treated for CD and 12 patients for cortisol producing adrenal adenoma was compared to 55 controls, matched for age, gender and educational level. Cognitive function was studied using standardized neuropsychological testing the Attentional Network Test. Median (interquartile range) duration of remission was 13 (5-19) years. In a multivariate analysis, attention, spatial orienting, alerting, working memory, verbal fluency, and reading speed were all diminished in comparison to controls, independent of scores for affective disorder and fatigue (figure 2). No overall difference in outcome was seen between patients in long-term remission for CD and cortisol-producing adrenal adenoma. Furthermore, the results on most cognitive tests were similar for patients with and without hormone deficiency, previous radiotherapy, and GC replacement. The results from our study demonstrate two important findings. Firstly, cognitive function is not only temporarily affected at short-term follow-up, but seems to be a permanent state. Secondly, patients with CS in remission have impairment in various domains of cognitive function and not only in hippocampal function which has previously received greatest attention.

The aetiology of cognitive dysfunction in patients with CS
The reason for the neurocognitive impairment in patients with CS is not clearly understood. It is also surprising how differently the postoperative course evolves in patients with CS. Some patients experience recovery relatively shortly after surgery while for others it can take years. Unfortunately, there are also patients that after many years in remission are still suffering from the distressing sensation of chronic fatigue and impaired general well-being. The reason for this discrepancy is unknown. Potential explanations include concomitant neuropsychiatric problems such as anxiety and depression, noted in up to 24% of patients one year after curative treatment\(^5\), inadequate replacement therapy of postoperative hormone deficiencies commonly seen after TSS\(^1\)\(^-\)\(^4\), and consequences of pituitary radiation therapy. In our study, none of these potential confounders were found to have a statistically significant impact on cognitive performance\(^4\). The number of patients in the subgroup analyses was, however, small and the results should be interpreted with caution. Another possible explanation could be a general effect of the pituitary disease \textit{per se}. However, when patients with CD in remission are compared with patients having other forms of pituitary diseases, cognitive function\(^6\) and QoL\(^4\) is significantly worse in the former group, arguing against that the pituitary disease itself plays a major role in this context. Thus, our results\(^4\) in addition to the two other recently published papers\(^6, 61\), suggest that long-term exposure to excess GC plays a causative role in the long-term cognitive consequences of CS.

GCs have a great impact on the central nervous system through its binding and activation of the GC receptor which is expressed widely in the brain\(^6\). GCs also activates the mineralocorticoid receptors that are found in more restricted areas such as the hippocampus, amygdala and pre-frontal cortex - collectively referred to as the limbic system. The limbic system is of great importance for cognitive function. The hippocampus is the main centre for memory and learning. The amygdala is the principal emotional centre while the prefrontal cortex is involved in behavioural inhibition, decision-making, executive function and working
memory. The enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) type 1, an enzyme that converts the inactive metabolite cortisone to the active compound cortisol, is also widely distributed in the brain. On the other hand, 11β-HSD type 2, with the opposite function, is only scarcely expressed. During states of GC excess, the protective role of 11β-HSD type 2 is therefore absent, and areas that express GC and mineralocorticoid receptors abundantly, such as the limbic system, may therefore be especially vulnerable. In rodents, short term GC administration leads to atrophy of dendrites in hippocampal neurons, changes that are reversible when GCs are withdrawn. Longer exposure to high GC levels causes hippocampal degeneration, partly due to loss of neurons. These observations support that the cognitive dysfunction observed in patients with CS may be caused by irreversible changes in the central nervous system. In a study on 18 patients with CS in remission, evaluated with proton magnetic resonance spectroscopy 8.5 ± 3.2 years after successful treatment, brain metabolites in the left and right hippocampus were measured. In comparison to healthy controls, concentrations of N-Acetyl-aspartate were lower and concentrations of glutamate and glutamine higher in patients with CS in remission, suggesting neuronal dysfunction/loss and glial proliferation (as a repair mechanism after neuronal dysfunction), respectively.

Patients with mild dementia and Alzheimer’s disease have increased endogenous cortisol production. In patients with neurodegenerative diseases, analysis of biomarkers in cerebrospinal fluid is useful in the clinical work-up and differentiates between different forms of dementias. In patients with CS in remission the pattern of neurodegenerative and inflammatory biomarkers in cerebrospinal fluid does not differ from healthy subjects. The underlying mechanism of the cognitive deficits seems therefore to be different from those seen in neurodegenerative disorders.
It has been suggested that the duration of active CS and the degree of hypercortisolism - *i.e.* patients who have had a longer duration of, or more extensive, hypercortisolaemia may have worse outcomes. In fact, lower BMD\textsuperscript{35}, adverse cardiovascular risk\textsuperscript{30}, increased mortality\textsuperscript{73} as well as worse cognitive function and reduced hippocampal volume\textsuperscript{61} have all been demonstrated to be associated with longer duration of hypercortisolaemia. Exploring this topic is however methodologically difficult for number of reasons. Firstly, endogenous CS is a rare disorder and designing a sufficiently powered study for this reason would be difficult. Secondly, it is difficult to estimate the duration of time with active disease. This will always be done retrospectively and since the symptoms and signs of CS usually develop insidiously, the exact time-point of debut is difficult to estimate. In addition, there is a risk that patients with the greatest suffering overestimate their time with active CS. Thirdly, the evaluation of the extent of hypercortisolemia is difficult. Both urinary free cortisol and serum cortisol can vary from one time to another and are, moreover, generally not good predictors of GC exposure in the tissues. An ideal method would be a measurement of tissue response to GC, a method that currently does not exist.
Management of patients with Cushing’s syndrome in remission

“He had been pleading for an exploratory operation which was considered impracticable, but in view of the growing conviction that his trouble must be due to a basophil adenoma, which might conceivably be amenable to radiation, he was given four x-ray treatments1.”

All patients who are treated for CS need oriented long-term follow-up by a qualified physician. Practically, the postoperative management can be divided into three different stages with different focus and challenges; i) an immediate postoperative management, ii) a GC dose tapering stage and iii) long-term management (Table 2).

Phase 1 - Immediate postoperative management - First 1-2 weeks after treatment

Within a week after TSS for CD, achievement of remission should be evaluated. Although no consensus exists, a low postoperative serum cortisol concentrations (<50 nmol/L), measured after a temporary cessation of GC replacement, is commonly thought to be compatible with remission10, 13, 74-76. During the early postoperative phase there is no need to perform ACTH test, and in fact, should be avoided since false positive cortisol response may be expected. In surgically treated patients with cortisol producing adrenal adenoma, assessment of remission is not required.

Almost all CS patients who achieve remission need GC replacement, both after TSS and adrenalectomy. From the published literature the initial dose of hydrocortisone given to patients with CS in early remission varies between 20 and 30 mg per day77, 78. The initial hydrocortisone dose given to children at the National institute of health is 8-12 mg/m2 in two divided doses79. In adults doses between 12 and 15 mg/m2 have been recommended10.
At our institute, all patients with CS receive parenteral hydrocortisone the first two days after TSS surgical treatment and are thereafter switched to tablets. On postoperative day 4-6, after hydrocortisone withdrawal for 24 hours, evaluation of remission is performed in patients treated for CD by measuring serum cortisol. If remission is confirmed, hydrocortisone is reintroduced. The decline in circulating levels of cortisol after successful treatment for CS is often dramatic. Postoperatively a substantial number of patients do therefore, despite GC replacement, experience symptoms compatible with GC deficiency, a phenomenon called steroid withdrawal syndrome. Occasionally these symptoms can be misinterpreted as a true GC deficiency and, subsequently lead to administration of unnecessarily high GC doses. In our experience, the hydrocortisone doses that are initially required vary, ranging between 20-40 mg per day in two divided doses. In general, patients with high preoperative urinary free cortisol require higher hydrocortisone doses (30 mg per day) and patients with normal or moderately elevated urinary free cortisol require lower doses (20 mg per day). In a small subgroup of patients with severe steroid withdrawal syndrome, initial hydrocortisone doses as high as 40 mg per day may be required.

All patients in remission who require GC replacement are thoroughly informed about the need of increased GC dose during intercurrent illness and receive a medical emergency card (figure 3).

Active CS is frequently accompanied by hypogonadism and central hypothyroidism. Since gonadal and the thyroid function normalizes in the majority of the patients during the first few months postoperatively, only patients with overt hypothyroidism and/or hypogonadism should receive replacement therapy in the immediate postoperative period.
Phase 2 - GC dose tapering - First 1-2 years after treatment

In patients with CS in remission, GC doses should be successively tapered with the ultimate goal to regain normal hypothalamus-pituitary-adrenal (HPA) axis function. In a retrospective study on 32 patients with CS in remission, 12 of 18 patients with CD recovered within a median follow-up time of 24 months (range 7-54 months) whereas six did not recover within 3-12 years\textsuperscript{77}. Eleven of 14 patients with cortisol producing adenoma recovered within 24 months (10-48 months) whereas three did not recover within 4-10 years. In another study on patients with CD a median time of 15 months (range 9-22 months) was required to recover a normal cortisol response to ACTH stimulation and 19 months (range 12-24 months) to allow discontinuation of hydrocortisone\textsuperscript{87}.

In previous studies various GC tapering schemes have been used\textsuperscript{77-79}. In our experience it is highly individual how fast GC tapering can be done and should mainly be guided by clinical status of the patient. In general, the initial hydrocortisone dose should be reduced by 5 mg every 3-6 weeks until a near-physiological dose of 10-20 mg per day has been reached. Thereafter ACTH-stimulation, after temporary interruption of GC treatment for 16-24 hours, should be performed every 3-6 months to evaluate recovery of the HPA axis. When unstimulated or stimulated serum cortisol exceeds 500 nmol/L, hydrocortisone replacement should be discontinued\textsuperscript{10}.

During the GC tapering period, and after discontinuation of hydrocortisone, patients experience symptoms due to the-steroid withdrawal syndrome\textsuperscript{80}. Subjectively the symptoms cannot clinically be differentiated from true GC deficiency, \textit{i.e.} fatigue, abdominal discomfort, nausea, muscle weakness and arthralgias. Again, symptoms due to the steroid
withdrawal syndrome may therefore lead to administration of unnecessarily high GC doses for too long periods of time. Thus, a major challenge during this stage is to differentiate between the withdrawal symptoms and symptoms of adrenal insufficiency. Objectively, steroid withdrawal syndrome is characterized by normal concentrations of cortisol in serum and normal urinary cortisol excretion while GC deficiency is accompanied by low cortisol concentrations. Furthermore, withdrawal symptoms usually improve or resolve within few weeks after dose reduction. In patients who experience the withdrawal symptoms unacceptably distressing, a temporary dose increment can be considered with a new trial of dose reduction 3-6 weeks later.

During the period of GC tapering, biochemical and or clinical signs of recurrence of CS should be simultaneously monitored. In patients with suspected recurrence, hydrocortisone should be discontinued and urinary free cortisol measured and dexamethasone suppression test performed. Similarly, patients with subnormal thyroid and gonadal status during the immediate postoperative period should receive regular monitoring of their anterior pituitary function.

**Phase 3 - Long-term management**

Due to the relatively high risk for recurrence after an initially successful surgery for CD\textsuperscript{15,18,19}, patients should be evaluated clinically and biochemically at least annually to confirm sustained long-term remission. Since recurrence can occur even decades after treatment, a lifelong follow-up is needed\textsuperscript{18}. Although late recurrence after unilateral adrenalectomy is rare, a long-term surveillance for cortisol producing adrenal adenoma has also been recommended\textsuperscript{88,89}. The current standard criteria of evaluating remission are based on a
normal urinary free cortisol and/or a normal suppression of the HPA axis using the low dose
dexamethasone suppression test. These criteria do, however, not take into consideration if
normal cortisol diurnal rhythm and the response of the HPA axis during psychological and
physical stress are restored. For patients with confirmed recurrence, additional treatment is
required (reoperation, radiotherapy or medical therapy)\textsuperscript{20}.

Pituitary hormone deficiencies are relatively common after TSS\textsuperscript{11-14}. Patients with
hypopituitarism have increased cardiovascular morbidity and mortality\textsuperscript{90, 91}. The cause is
probably multi-factorial; the unfavourable metabolic profile due to GH deficiency\textsuperscript{92}, the
quality of gonadal replacement, treatment with pituitary radiotherapy\textsuperscript{93} and underlying
diagnosis of CD\textsuperscript{94} may all be important factors. A thorough evaluation of pituitary function is
therefore mandatory in all patients with CS in remission and adequate hormone replacement
should be initiated when indicated.

GH secretion is compromised in patients with CD for a long period after remission has been
achieved\textsuperscript{16, 17}. Evaluation of GH deficiency should therefore not be performed earlier than 1 or
2 years after successful treatment\textsuperscript{95}. In patients with confirmed GH deficiency, replacement
therapy should be strongly considered as QoL and cognitive function are negatively affected
by GH deficiency and improves with GH replacement\textsuperscript{96-98}. Furthermore, patients with CS in
remission who also have GH deficiency, improved metabolic profile have been demonstrated
with GH replacement\textsuperscript{96}.

Between 25 and 51 per cent of patients treated for CS require chronic GC replacement
therapy, both patients treated for CD and cortisol producing adrenal adenoma\textsuperscript{49, 54, 77, 79}. The
relative risk of death in patients with primary adrenal insufficiency receiving GC replacement
therapy is 2-fold higher than in the background population\textsuperscript{99, 100}. Patients with acromegaly and
ACTH insufficiency who receive a daily hydrocortisone dose of more than 25 mg per day have increased mortality\textsuperscript{101}. Hence, there are indications that GC replacement may influence mortality in patients with adrenal insufficiency. It has been shown that the endogenous cortisol production is approximately 10 mg/m\textsuperscript{2} per day, corresponding to 15-20 mg of oral hydrocortisone\textsuperscript{102}. Adverse metabolic profile\textsuperscript{103}, lower BMD\textsuperscript{104, 105} and impaired QoL\textsuperscript{106, 107} have all been associated with high GC replacement doses. In GC replaced patients with hypopituitarism, receiving a mean hydrocortisone dose of 24 mg, a dose-related increase in BMI, triglycerides, and total- and low-density lipoprotein cholesterol concentrations was demonstrated\textsuperscript{103}. Also, as recently indicated, the cortisol exposure time profile during GC replacement may also be important for the metabolic outcome\textsuperscript{108}. For patients with CS in remission who have adrenal insufficiency, supraphysiologic GC doses should therefore be avoided. This is often difficult to avoid in the immediate postoperative phase, but the dose should be brought down to physiological daily doses as fast as possible. Simultaneously, GC doses should not be tapered too fast and the long-term maintenance dose should not be too low risking acute adrenal crisis. In fact, patients with hypopituitarism and concomitant ACTH deficiency may have excess mortality due to adrenal crisis in response to acute stress and intercurrent illness\textsuperscript{109}.

The cardiovascular risk profile should be evaluated at least yearly in all patients who have been treated for CS by measuring weight, height, body mass index, waist circumference, blood pressure, lipid profile and fasting glucose. When hypertension, hyperglycaemia and dyslipidemia are present these should be adequately treated. A more aggressive approached should be considered for patients with CS in remission in accordance with guidelines for other high risk groups such as diabetes mellitus\textsuperscript{110} and has been suggested for patients with acromegaly\textsuperscript{111}.
Patients with pituitary insufficiency also have reduced BMD and an increased fracture rate\textsuperscript{112-115}. Among many potential explanations for these observations is the use of supraphysiological GC doses, inadequate sex hormone replacement therapy and untreated GH deficiency\textsuperscript{116}. Bone health should therefore be regularly evaluated in patients with CS in remission and management for osteoporosis initiated when indicated.

Reduced QoL, cognitive dysfunction and chronic fatigue is still present in a substantial number of patients with CS in remission despite apparently adequate hormonal replacement therapy or in hormonally intact patients\textsuperscript{39, 49, 60, 61}. In the most severely affected patients the neuropsychological problems results in decreased working capacity and social isolation\textsuperscript{49}. An assessment of potential cognitive impairments and/or psychiatric disorders should be performed annually by evaluation of subjective complains of fatigue, memory impairments, concentration difficulties, attention deficits, anxiety and/or depressed mood. In cases where psychiatric disorders are suspected, oriented evaluation should be performed and when disorders such as depression and/or anxiety are present these should be promptly treated. Unfortunately, at present there is no specific treatment available that alleviates the cognitive dysfunction or fatigue in patients with CS in remission. It is however important to rule out other treatable causes such as hypopituitarism, other endocrine disorders, hormonal overtreatment, vitamin deficiencies and psychiatric disorders. Supporting is also important, \textit{i.e.} that the patients are heard and that they feel that the caregiver understands their distressing problems. It has been reported that patients with CD in remission use different and less effective coping strategies compared with healthy controls\textsuperscript{117}. Indeed, their coping is less active and they seek social support less often than controls. Patients with CS in remission
should therefore be encouraged to use more active coping strategies and to seek social support\textsuperscript{117}.

\textbf{Conclusion}

In recent years, several studies have demonstrated that patients with CS in remission have adverse cardiovascular risk profile, bone health, impaired QoL and cognitive dysfunction, even many years after successful treatment. In accordance with the diagnostic work-up and management of patients with active CS, an oriented long-term follow-up plan by a qualified medical team is required for all patients who are successively treated for CS. Careful information about each stage in the management should be provided; i.e. the immediate postoperative period, the GC dose tapering stage and the long-term follow-up.

\textbf{Disclosure}: Oskar Ragnarsson has nothing to declare. Gudmundur Johannsson is consultant for Viropharma and Astra Zeneca and has received lecture fees from Novo Nordisk, Eli Lilly, Merck Serono, Otsuka and Pfizer. This work has not received any specific funding.
References


3. Albright F. Cushing’s syndrome; its pathology and physiology, its relationship to the adrenogenital syndrome, and its connection with the problem of the reaction of the body to injurious agents. Harvey Lect. 1943 38 123-186.


83. Mathioudakis N, Thapa S, Wand GS & Salvatori R. ACTH-secreting pituitary microadenomas are associated with a higher prevalence of central hypothyroidism compared to other microadenoma types. Clin Endocrinol (Oxf) 2012 77 871-876.


Legends to figures

**Figure 1.** Results from a cross-sectional study on quality of life in 343 patients with Cushing’s syndrome in remission (mean ± SD time in remission 11.8 ± 4.9 years). Data are presented as mean ± 95% confidence intervals. Patients with Cushing’s syndrome in remission had lower scores on all individual domains of the short-form 36 questionnaire compared to age- and sex-matched control values from the US population (zero-line). (From Lindsay JR, Nansel T, Baid S, Gumowski J & Nieman LK. Long-term impaired quality of life in Cushing's syndrome despite initial improvement after surgical remission. J Clin Endocrinol Metab 2006 91 447-453. Adapted with permission from Endocrine Society)

**Figure 2.** Results from a cross-sectional study on cognitive function in 55 patients with Cushing’s syndrome (CS) in remission (median (interquartile range) duration of remission 13 (5-19) years) and 55 healthy controls, matched for age, gender and educational level. The bar charts demonstrate median score on a) trail making test A, b) trail making test B (visual scanning, divided attention and motor speed), c) digit symbol coding test (speed processing) d) digit span test (auditory attention and working memory), e) spatial span test (visual attention and working memory), f) verbal fluency test, and g) reading speed test, in patients with Cushing’s syndrome in remission. P-values are obtained from multiple regression analysis adjusted for scores for fatigue, depression and anxiety. Error bars represents 95% confidence interval. (from Ragnarsson O, Berglund P, Eder DN & Johannsson G. Long-Term Cognitive Impairments and Attentional Deficits in Patients with Cushing's Disease and Cortisol-Producing Adrenal Adenoma in Remission. J Clin Endocrinol Metab 2012 97 E1640-1648. Reproduced with permission from Endocrine Society)

**Figure 3.** The Swedish medical emergency card for patients with adrenal insufficiency. (From Dahlqvist P, Bensing S, Ekwall O, Wahlberg J, Berghordsdottir R & Hulting AL.)
### Table 1. Summary of studies on cognitive function in patients with Cushing’s syndrome in remission

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<td>Mauri et al. 1993</td>
<td>25 CD Italy</td>
<td>Memory, learning, visual scanning, divided attention, motor speed, information-processing speed and verbal fluency</td>
<td>Prospective</td>
<td>Pre- and post treatment (8 of 25 patients re-evaluated 6 months after treatment)</td>
<td>Eight patients re-tested 6 months after treatment showed significant improved memory and attention but not in other cognitive functions compared to controls.</td>
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<td>Dorn et al. 2000</td>
<td>29 CD USA</td>
<td>Memory, learning, problem solving, motor speed, visual construction ability and IQ</td>
<td>Prospective</td>
<td>Pre-treatment and at 3, 6 and 12 months after treatment</td>
<td>No significant improvement in cognitive functioning. Trend of lower IQ at baseline. For some subscales of IQ there was a positive relationship with recovery of the HPA axis and a negative relationship with duration of CS</td>
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<td>3 EAS</td>
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<td>Forget et al. 2002</td>
<td>9 CD Canada</td>
<td>Attention, visual processing, visuospatial processing, memory, reasoning and verbal fluency</td>
<td>Prospective</td>
<td>Pre-treatment and 1 year after treatment</td>
<td>Visual processing and verbal fluency improved after treatment but no other cognitive functions.</td>
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<td>4 CPAA</td>
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<td>Hook et al. 2007</td>
<td>27 CD USA</td>
<td>Memory, learning, attention, working memory and verbal fluency</td>
<td>Prospective</td>
<td>Pre-treatment and at 3-5, 6-12 and 13-18 months after treatment</td>
<td>Memory, learning and verbal fluency improved after treatment while attention and working memory did not.</td>
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<td>Tiemensma et al. 2010</td>
<td>74 CD Netherlands</td>
<td>Global cognitive functioning, memory, learning, working memory and verbal fluency</td>
<td>Cross-sectional</td>
<td>Mean ± SD duration of remission 13 ± 13 years (range 1-51 years)</td>
<td>Patients with CD had worse global cognitive functioning, memory, learning, working memory and verbal fluency compared with patients with NFPA</td>
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<td>54 NFPA</td>
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<td>Resmini et al. 2012</td>
<td>25 CD Spain</td>
<td>Visual and verbal memory</td>
<td>Cross-sectional</td>
<td>11 of 33 patients had active CS. Mean ± SD duration of remission for the remaining 22 was 5.5 ± 3.7 years</td>
<td>Memory performance did not differ between active CS and CS in remission. Verbal and visual memory worse in CS patients (active and in remission pooled) in comparison to controls.</td>
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<td>Ragnarsson et al. 2012</td>
<td>43 CD Sweden</td>
<td>Working memory, attention, information-processing speed, verbal fluency, reading speed, alerting, orienting, and executive control</td>
<td>Cross-sectional</td>
<td>Median (interquartile range) duration of remission was 13 (5–19) yr</td>
<td>Attention, spatial orienting, alerting, working memory, verbal fluency, and reading speed all worse in comparison to controls, independent of scores for depression and anxiety and fatigue.</td>
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<td>12 CPAA</td>
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CD = Cushing’s disease; CPAA = Cortisol producing adrenal adenoma; CS = Cushing’s syndrome; EAS = Ectopic ACTH syndrome; HPA = Hypothalamus-pituitary-adrenal; IQ = Intelligence quotient; NFPA = Non-functioning pituitary adenoma; SD = Standard deviation
Table 2. Summary of the three phases of postoperative management of surgically treated patients with Cushing’s syndrome

| Immediate postoperative management (First 1-2 weeks after treatment) | • Evaluate if remission has been achieved by measuring serum cortisol at 7-9 AM, after hydrocortisone withdrawal for 24 hours.  
• Cortisol concentrations below 50 nmol/L are compatible with remission and low risk for recurrence.  
• Introduce GC replacement to successfully treated patients with initial hydrocortisone dose of 20-40 mg per day in 2-3 divided doses.  
• Inform the patient about the risk for development of the steroid withdrawal syndrome.  
• Give thorough information on the need of increased GC dose during intercurrent illness.  
• Evaluate anterior and posterior pituitary function. |
| --- | --- |
| GC dose tapering stage (First 1-2 years after treatment) | • Reduce the initial hydrocortisone dose by 5 mg every 3-6 weeks until a physiological dose of 10-20 mg per day has been reached.  
• Thereafter, perform ACTH-stimulation every 3-6 months to evaluate recovery of the HPA axis.  
• When unstimulated or stimulated serum cortisol exceeds 500 nmol/L, hydrocortisone replacement should be discontinued.  
• Inform the patient about the risk for development of the steroid withdrawal syndrome during dose tapering. Symptoms due to steroid withdrawal need to be differentiated from symptoms of adrenal insufficiency.  
• Give thorough information on the need of increased GC dose during intercurrent illness. |
| Long-term management | • Evaluate biochemical and/or clinical signs of recurrence of CS at least annually.  
• Assess menstrual cycle, sexual functions and pituitary function tests at least yearly and initiate adequate hormone replacement when indicated.  
• Consider evaluation of possible growth hormone deficiency 1-2 years postoperatively.  
• For patients with remaining adrenal insufficiency, avoid supraphysiological GC replacement doses.  
• Evaluate cardiovascular risk profile yearly and treat hypertension, hyperglycaemia and dyslipidemia when present.  
• Evaluate bone health regularly ant treat osteoporosis when indicated.  
• Assess potential cognitive impairments and/or psychiatric disorders annually by evaluating subjective complains of fatigue, memory impairments, concentration difficulties, attention deficits, anxiety and/or depressed mood  
• When cognitive dysfunction is present rule out treatable causes such as hypopituitarism, other endocrine disorders, hormonal overtreatment, vitamin deficiencies, depression and/or anxiety.  
• Support patients with cognitive impairment and discuss coping strategies and social support. |
Figure 3.

IMPORTANT
MEDICAL INFO.

THIS PATIENT NEEDS DAILY REPLACEMENT THERAPY WITH CORTISONE.

In case of serious illness, vomiting or diarrhoea, hydrocortisone 100 mg iv/im and iv saline infusion should be administered without delay.

Swedish Endocrine Society

__________________________
Name

__________________________
Personnummer / Date of birth