Lessons from rare diseases: pathophysiology of stress-related diseases and organization and evaluation of care for patients with Cushing's syndrome

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CHAPTER 10

GENERAL DISCUSSION AND SUMMARY

Stress is a psychophysiological response to difficult or challenging situations and to physical as well as psychological stressors.[1, 2] The endocrine system, and especially the stress hormone cortisol, play an important role in regulating the stress response.[3] Between 20 to 40 minutes after the initiation of a stressful event, cortisol secretion peaks, amongst others resulting in releasing energy stores by elevating blood glucose levels to provide metabolic 'fuel' for the body, and inhibiting non-essential functions such as aspects of immune system, digestive system, and reproductive system, permitting other systems like the sympathetic nervous system and certain psychological systems necessary to overcome threat to function effectively.[4] Cortisol is essential for survival, however prolonged stress and prolonged exposure to increased cortisol concentrations lead to tissue damage and disease, and consequently, adversely affect multiple vital organ systems.[2] In Cushing's syndrome (CS), cortisol is produced excessively, whereby prolonged and excessive hypercortisolism is associated with increased morbidity and mortality, and decreased quality of life.[5-8] Central serous chorioretinopathy (CSC), a specific form of macular degeneration, is another disorder in which stress and cortisol are believed to be involved in the pathophysiology, in this case by playing a possible role in triggering the development of the disease.[9-11] In CSC, thickening, hyperpermeability and choroidal congestion damage the retinal pigment epithelium, inducing serous subretinal fluid accumulation and subsequently detachment of the neuroretina.[9, 12, 13] Thus, both CS and CSC are rare conditions in which the activity of the hypothalamus-pituitary-adrenal (HPA)-axis and cortisol play a key role. This thesis addresses the pathophysiology of stress related diseases, taking the aforementioned rare diseases as a model for stress vulnerability of the brain (CS) and the eye (CSC). The second aim of this thesis was to describe the organization of thromboprophylaxis management, and the outcome evaluation and quality of care for patients treated for CS. **Chapter 1** provides a general introduction to the regulation of the stress response, the rare conditions of CS, and CSC, and discusses the underlying rationale for the studies presented in this thesis.

PART ONE

In **chapter 2**, a detailed ophthalmological screening with multimodal imaging including optical coherence tomography (OCT) was performed in a series of consecutive patients with active CS without visual complaints, in order to evaluate possible subclinical abnormalities within the CSC spectrum and the potential need for standardized ophthalmological evaluation of all CS patients. Of the 11 patients included, three patients showed abnormalities reminiscent of (subclinical) CSC. One patient was subsequently diagnosed with active CSC, including macular subretinal fluid on OCT, and was successfully treated with half-dose photodynamic therapy. In one other patient OCT revealed a unilateral pseudovitelliform lesion and on fluorescein angiography hyperfluorescent changes were seen, while the third patient showed unilateral leakage on fluorescein angiography. Therefore, retinal abnormalities resembling (subclinical) CSC in patients with CS may exist even in the absence of visual complaints, and might be more common than previously thought.

Clinical implications: Because of the therapeutical consequences aimed at prevention of loss of vision, clinicians/endocrinologists should actively question patients with CS about any visual complaints and apply a low threshold for referring patients for ophthalmological evaluation. We

advocate that routine screening of all newly diagnosed patients with CS for abnormalities within the CSC spectrum should be a topic of a future multi-center, prospective cohort study.

Vice versa, since a relationship is presumed between stress and the onset of CSC,[9-11] and CSC can be the presenting symptom of CS,[14] it is relevant to question whether patients with CSC should be screened for CS. In **chapter 3,** a systematic screening for the presence of CS in a large cohort of chronic CSC patients is presented, aiming to assess the prevalence of CS in patients with chronic CSC, and to assess whether chronic CSC is associated with hyperactivity of the HPA-axis. None of the 86 included chronic CSC patients met the clinical or biochemical criteria of CS. However, the activity of the HPA-axis was increased in patients compared to healthy controls, as reflected by higher 24 hour urinary free cortisol (within the normal range) with a mean difference of 32 nmol/24 hour, and accompanying higher waist circumference and diastolic blood pressure. Circadian, diurnal cortisol rhythm was preserved in CSC patients. Furthermore, in contrast to earlier studies suggesting an association between CSC and psychosocial stress,[11, 15-17] CSC patients did not report more stress or stress-related problems using validated questionnaires. In addition, no associations were found between HPA-axis activity, CSC activity and psychosocial stress.

Clinical implications: Based on these results, routine screening for CS in all CSC patients is clearly not indicated. Since the interpretation of the biochemical screening tests in light of the clinical features is often challenging and in order to minimize false positive test results, screening should be reserved for CSC patients with additional clinical signs and symptoms raising the suspicion of hypercortisolism. However, the results of the study clearly indicate increased activity of the HPA-axis in CSC patients when compared to controls, although this is not accompanied with the perception of more psychosocial stress. This observed higher activity of the HPA-axis is in concordance with the previously reported association between cortisol and CSC, yet further studies are needed to unravel the underlying pathophysiological mechanisms and the role of stress and stress-reducing interventions in the onset and clinical course of CSC.

The activity of the HPA-axis as a warrant of endogenous exposure to stress and cortisol can be determined with a number of different tests, all reflecting different aspects of secretion and exposure to cortisol. Concentrations of cortisol in scalp hair can be measured to estimate long-term cortisol exposure. In order to investigate the suspected relationship between cortisol and chronic CSC, hair cortisol concentrations in a large cohort of 48 chronic CSC patients, participating in the afore described study on HPA-axis evaluation in CSC, were evaluated and compared to the concentrations of hair cortisol of adult controls from the general population (**chapter 4**). Increased hair cortisol concentrations were present in 4% of patients with CSC and in 6% of the controls, and the mean hair cortisol concentration was not different between the two groups. This finding questions the previously reported suggestion of HPA-axis hyperactivity in CSC, however, the assessment method using hair cortisol concentrations most probably capture a different aspect of cortisol exposure then the biochemical evaluations used in other studies (e.g. 24 hour urinary free cortisol or salivary cortisol levels). We propose that either the hair cortisol concentrations technique is not sensitive enough to detect minor and perhaps short-term elevations in cortisol levels within

the normal range, keeping in mind the large individual variation in normal cortisol levels and glucocorticoid sensitivity, or minor increases in cortisol concentrations at tissue level leading to the specific CSC alterations are not reflected by increased concentrations of cortisol in hair. One could also argue that the long-term cortisol exposure is not increased in CSC, however a short peak or prolonged temporary elevation in cortisol levels in sensitive subjects may be sufficient to induce the retinal alterations characteristic of CSC. This hypothesis is supported by the described appearance of CSC after short-term steroid treatment.[10] Based on these novel observations, it is also plausible to assume that the relationship between CSC and cortisol is not as straightforward as previously thought. Furthermore, no correlation between hair cortisol concentrations and urinary free cortisol levels was seen in patients with chronic CSC, despite the reported strong correlations between hair cortisol concentrations and urinary free cortisol levels in patients with CS.[18, 19] Finally, no difference in hair cortisol concentrations was found between patients with active CSC disease compared to patients with inactive disease, indicating the absence of an association between disease severity and hair cortisol concentrations.

Clinical implications: Hair cortisol concentrations in patients with CSC are not elevated compared to population-based controls, and no association between hair cortisol concentrations and CSC severity was found. Therefore, hair cortisol concentrations are not useful in monitoring CSC disease activity.

Along with biochemical stress as reflected by HPA-axis hyperactivity, also psychosocial stress and 'type A' behavioural aspects are described to be associated with CSC. [11, 16, 20] In order to identify potentially modifiable psychosocial aspects in support to the current standard treatment, **chapter 5** reports on a cross-sectional study in a cohort of 86 patients with chronic CSC using validated questionnaires to capture the presence of possible maladaptive personality traits (i.e. traits related to type A behavioural pattern), apathy and irritability, and coping strategies. Patients' findings were compared to both Dutch population based reference data and data from patients treated for Cushing's disease. Psychological morbidity in the form of apathy and irritability was not increased in CSC patients. In addition, maladaptive personality traits such as type A behavioural characteristics were not more prevalent in patients with CSC compared to the general population. These are intriguing findings because they contradict what has been suggested in previous studies.[16, 21-23] However, in these studies, behavioural characteristics were mainly assessed using behavioural outcome measures, showing no correlation with personality characteristics and psychopathology[24], and type A behavioural characteristics were not strictly defined.

CSC patients make more use of certain coping strategies (e.g. passive coping, seeking social support, and in males also active coping). Remarkably, though not statistically significant, the personality profile, psychological morbidity, and coping characteristics of CSC patients were more comparable to features of treated Cushing's disease patients than to the population-based data. Because patients treated for Cushing's disease have been exposed long-term to excessive cortisol levels, these patients can be regarded as a human model to study the effects of cortisol excess, amongst others, on personality and behaviour. Maladaptive personality traits and psychological morbidity such as apathy and irritability have been well described in patients with

Cushing's disease.[25, 26] In line with the biochemical resemblance of an activated HPA-axis in both CSC (slightly activated HPA-axis) and Cushing's disease (excessive activation of the HPA-axis) as mentioned above, this study also showed a relative similarity regarding the spectrum of personality features.

Clinical implications: Ophthalmologists often assume and report stress-related and type A behavioural characteristics in CSC patients,[16, 21, 22] and therefore stress-reduction and interventions targeting personality traits are common in clinical management strategies.[27-29] However, based on the results of the present study, these interventions may not be useful. Yet, the use of certain coping strategies could be a point to address in psychosocial care and self-management programs.

PART TWO

The second part of this thesis focused on the organization, outcome, and quality of care for patients with CS. **Chapter 6** systematically reviewed the literature to investigate whether mortality remains increased in patients biochemically cured of Cushing's disease. In addition, a meta-analysis was performed, including follow-up studies reporting the standardized mortality ratio (SMR) for patients cured from Cushing's disease after initial treatment. A total of 766 patients that were included in eight studies were included in the meta-analysis. Seven out of the eight studies showed a SMR above 1.0, with a pooled SMR of 2.5 (95% CI 1.4 - 4.2) when including all studies. Also, when a sensitivity analysis excluding two outliers was performed, the SMR remained increased. This means that mortality remains increased in patients with Cushing's disease even after initial biochemical remission, suggesting that cure does not fully reverse the metabolic effects of long-term exposure to cortisol excess. Unfortunately, applying meta-regression techniques to assess potential causes of increased mortality was not possible due to the lack of individual patient characteristics stratified by cure status. However, it is plausible that adverse effects of the disease and/or its treatment such as hypopituitarism contribute to the persisting increased mortality risk, although the percentage of post-treatment hypopituitarism could not be extracted from the studies. Furthermore, the results of the meta-analysis are supported by evidence showing persistent multisystem morbidity after biochemical cure, since there is accumulating evidence that morbidity related to cortisol excess decreases after successful treatment of Cushing's disease, however does not normalize. A high prevalence of atherosclerosis and an increased cardiovascular risk are reported to maintain after curation, which are thought to be related to residual abdominal obesity and insulin resistance.[30] Also the risk for myocardial infarction and stroke in cured Cushing's disease patients is shown to remain increased during long-term follow-up,[31] and even an increased prevalence of psychopathology and cognitive impairments are documented.[25, 32]

Apart from the residual physical and psychological morbidity and increased mortality, patients biochemically cured from Cushing's disease also report persisting impairments in cognitive and executive functioning.[25, 33] Furthermore, a reduction in quality of life is reported to persist despite curation.[34] The question whether patients with remitted Cushing's disease also demonstrate altered performance and brain activity patterns with regard to cognitive planning and executive functioning, was assessed in **chapter 7** by means of functional magnetic resonance imaging, while

both patients and healthy controls complete a Tower of London task (parametric visuospatial planning task). Twenty-one cured Cushing's disease patients and an equal number of healthy gender-, age-, and level of education-matched controls were included. No differences were found in performance between the two groups, neither in number of correct trials, nor in response times per trial, or in the region of interest analysis. As previous studies revealed visuospatial impairments in active Cushing's disease patients,[35] our findings suggest that these impairments can improve after remission. Exploratory whole-brain analyses demonstrated increased brain activation in certain brain areas during the Tower of London task in remitted patients, indicating patients need to over-recruit these brain regions involved in higher cognitive processes to attain a similar performance level as healthy controls, and thus require more effort to successfully complete a visuospatial planning task.

Clinical implications: The persistently increased mortality risk despite remission of hypercortisolism suggests irreversible effects of long-term glucocorticoid excess exposure. It also seems that prolonged exposure of the brain to cortisol excess leads to permanent alterations in brain activation of certain regions, even after long-term remission. Cushing's disease may therefore result in long-term, irreversible, subtle scarring effects during (demanding) executive functioning tasks. These findings are important and of relevance to patients counseling in everyday clinical practice, but also to increase the awareness of the treating physician to provide good quality follow-up care with an eye for persisting complaints and comorbidity management.

During active hypercortisolism as well as in the postoperative period, and even after remission, an increased risk of venous thromboembolism has been consistently reported.[36-38] Evidence-based guidelines on prophylactic anticoagulation in these patients with such a rare condition are not available due to the absence of prospective treatment studies evaluating thromboprophylaxis effects on the occurrence of venous thromboembolism in CS. In the context of quality of care and evaluation of outcomes and complications, a clinical guideline addressing thromboprophylaxis management in patients with CS is currently a clear unmet need. A first step in conducting studies useful for guideline development, is to map the current clinical practice regarding this specific subject. **Chapter 8** aimed to map the current clinical thromboprophylaxis strategies in patients with CS across expert reference centers within the European Reference Network (ERN) on Rare Endocrine Conditions (Endo-ERN). These centers have specifically been endorsed as expert centers for the diagnosis and treatment of CS. The results of the online survey demonstrate that a large practice variation regarding thromboprophylaxis management in patients with CS still exists, even in the expert centers of Endo-ERN. Although the majority of the reference centers (23 out of 25) provided thromboprophylaxis to their patients, a standardized treatment protocol was available in only one center. Also the time of initiation and abrogation of thromboprophylaxis varied greatly between the centers.

Clinical implications: These results exemplify the need for a protocolled strategy for thromboprophylaxis in CS that will enable to assess the best, possibly even individualized, treatment options.

For quality and outcome evaluation purposes, an outcome evaluation method called Outcome Squared was recently developed by our center for patients surgically treated for pituitary tumors. This method unifies different outcome parameters in time, taking the balance between efficacy and safety into account, by including both remission and complications in a standard classification for multidimensional outcome evaluation.[39] Especially in Cushing's disease, for which transsphenoidal surgery is the first line treatment, both remission and complications determine the overall success of the procedure. Failure to achieve remission is potentially life threatening,[40] whereas complications such as hypopituitarism including adrenal insufficiency are also associated with comorbidities, increased mortality, and reduced quality of life.[41-44] **Chapter 9** reported on long-term integrated postoperative follow-up measures in patients with Cushing's disease using the Outcome Squared approach. Seventy-two consecutive patients treated by transsphenoidal resection were included. One year after surgery, 55.4% of the patients showed good outcome (remission without pituitary deficiencies excluding adrenal insufficiency), whereas in 4.6% poor outcome (no remission, pituitary deficiencies present) was observed. In 29.2% remission with pituitary deficiencies was observed, and 10.8% had persistent disease without pituitary deficiencies. When adrenal insufficiency was regarded as adverse outcome as well, in 17% good outcome after one year was reported, whereas 68% showed remission with the presence of pituitary deficiencies. With long-term follow-up, a gradual shift to the good outcome category occurred, mainly due to recovery of the HPA-axis. The results show that the majority of patients are in remission five years after transsphenoidal surgery (91%), some after successful re-interventions, though in a considerable number at the expense of persistent hypopituitarism (58% of patients in remission, partly explained by HPA-axis deficiency). Remission rates in this study are in line with previously published studies.[45-47] As might be expected due to the extent of the tumor and therefore a more extensive surgical procedure, macroadenoma patients more often showed new onset hypopituitarism or poor outcome when compared to patients with microadenomas. Also patients with an invisible/uncertain adenoma on preoperative MRI scan appeared to be at increased risk of poor outcome (no remission and persistent pituitary deficiencies).

Clinical implications: The four different integrated outcome quadrants used in the Outcome Squared method provide, for the first time, a uniform, patient-centred integrated overall view of the important balance between efficacy and safety of transsphenoidal surgery in Cushing's disease. The results of the subgroup analysis (e.g. microadenoma patients) can be used in the out-patient setting for individualised patient counselling. A health care provider can easily recognize patient groups with good or adverse outcomes and modify treatment strategies accordingly, if applicable. The results of this study also show that even after multiple and combined interventions remission without adverse effects can be achieved, and reinterventions thus also can be considered save procedures.

Future perspectives

Conducting prospective or randomized controlled clinical studies in rare diseases is often challenging, due to the small number of available patients, and the lack of available funding for these

trials. These studies however, are of utmost importance to improve insights in pathophysiology of the underlying condition and to improve treatments and quality of care, especially in an era in which evidence-based medicine has taken a flight, outcome evaluations are demanded by patients, society, and the profession, and evidence-based guidelines have become the cornerstone of clinical practice. And most importantly, the ultimate goal from a patients' perspective is to improve not only their prognosis, but first of all their quality of life. Because this thesis addresses two different rare diseases, as a model for stress vulnerability, suggestions for future research subjects with regard to both CS and CSC will be discussed below.

An increased activity of the HPA-axis as observed in CSC patients in our study, is in concordance with the previously reported association between cortisol and CSC. However, our study on hair cortisol concentrations in patients with CSC clearly demonstrated that the relationship between CSC and cortisol might not be as straightforward as previously thought. Further studies are required to unravel the underlying pathophysiological mechanisms, for example addressing inter-individual glucocorticoid sensitivity and differences in susceptibility to develop CSC, and the role of the mineralocorticoid receptor and glucocorticoid receptor, and their potential differential effects on gene expression in the pathogenesis of CSC. Furthermore, the studies described in this thesis did not find any rationale for interventions targeting personality features. It would, however, be of interest to future research whether altering coping mechanisms and reducing stress (and thereby potentially reducing HPA-axis activity) can improve the course of disease in CSC. Since it might be of clinical importance to routinely screen patients with CS for abnormalities within the CSC spectrum, further (prospective) studies on the prevalence and natural course of subclinical CSC are needed to assess whether incorporation of ophthalmological screening in the general clinical work-up of patients with CS is required.

This thesis has also shown that mortality remains increased in Cushing's disease, despite long-term biochemical remission. In order to improve survival in patients that have obtained long-term remission, future studies should focus on unraveling risk factors contributing to the increased mortality in these patients, and ultimately, studies on interventions addressing these risk factors should point out whether the increased mortality rates can be repulsed. With regard to alterations in brain activation of certain regions in remitted CS as was demonstrated in this thesis, longitudinal studies are needed to provide insight into the onset and time course of these alterations in brain activity patterns and cognition during active disease state and transition into remission, and to find out whether remission remits all (visuospatial) impairments. It would be of special clinical interest to find out whether the compensatory increased brain activity to normalize cognitive performance contributes to the reported persisting increased prevalence of mood related disorder, fatigue, decreased stress resilience in daily life, and reduced quality of life of patients with remitted CS. This should be captured by adding morbidity and quality of life related questionnaires to the longitudinal studies in order to associate the outcomes to the functional MRI data. In case a contribution of compensatory brain activity to morbidity is made plausible, the ultimate step would be to evaluate whether psychological interventions such as cognitive behavioral therapy addressing the balance between daily activities in need of the compensatory activities of certain brain areas and

activities that do not require these compensatory activities could be able to decrease complaints and increase quality of life.

With regard to thromboprophylaxis management in patients with CS, a first step in conducting studies required for guideline development on this topic was undertaken in this thesis by mapping the current clinical practice in expert centers endorsed for the diagnosis and treatment for this specific rare condition across Europe. Both patients and clinicians are in need for randomized controlled trials to establish the optimal prophylactic anticoagulant strategy (i.e. what would be the drug of first choice, when to start, when to stop, what to do with peri-operative thromboprophylaxis management, which patients are at increased risks of bleeding complications and how to adjust thromboprophylaxis treatment in these patients). Furthermore, future studies should assess additional risk factors to determine which patients are particularly at risk for venous thromboembolism and would benefit from thromboprophylaxis, in order to be able to carefully balance the known hypercoagulable state, potential additional risk factors for thrombosis, and increased risk of (perioperative) bleeding in daily clinical practice.

Treatment outcome evaluations should be performed to provide better insight in performance and quality of care, but also enable to identify predictors and moderators of outcome in order to develop the most effective treatments, gain insight into which treatment is best for which patient, and to provide the best individual patient counselling. The use of the Outcome Squared method can provide comparisons of outcomes of different treatment strategies, for example medical therapy versus radiotherapy in persistent disease, and other outcomes relevant to patients and their quality of life (e.g. symptomatology, burden of disease, functional outcome) can be incorporated in the four outcome categories by adjusting the definitions of intended and adverse effects. The method is also suitable to evaluate outcome of treatment strategies including multiple interventions rather than focusing on a single intervention. In future research, integrating outcomes using the Outcome Squared method can be used for the comparison between centres and studies, provided that identical definitions and outcome are used. In the field of pituitary diseases, we believe that the use of the Outcome Squared approach provides added value to the evaluation of the provided quality of care, however, international consensus is needed on the use of Outcome Squares in outcome evaluations to pursue comparability of studies that have a more detailed focus on outcome.

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