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CHAPTER 15

Summary & General discussion
Patients with pituitary disease in a stable medical condition demonstrate persistent morbidity. This thesis describes their health outcomes by using a biopsychosocial approach covering a continuum ranging from biological and physiological measures, to measures of general health perceptions, as described by the Wilson-Cleary model (1). In this chapter the Wilson-Cleary model will be elaborated for pituitary disease based on the health outcomes described in this thesis (Figure 1).

**Biological and physiological variables**

In clinical practice, endocrine diseases are diagnosed and followed by evaluating clinical signs and hormone measurements. Serum, plasma or urinary hormone concentrations are commonly used tools by clinicians to classify disease status in chronic care. It is well acknowledged that the currently available physiological measures do not always reliably represent the clinical situation. A main problem is that serum hormones do not reflect hormone action at the tissue level. Therefore, there is an unmet need for better biochemical measures reflecting organ specific physiological hormone action. In the present thesis, new/less commonly used biological factors – as examples of measuring hormone (action) at the tissue level - were assessed in patients with (previous) dysfunction of the HPA-axis, namely brain characteristics in patients with remission of Cushing’s disease, and scalp hair samples reflecting long-term cortisol exposure measured in patients with adrenal insufficiency.
Reviewing existing literature on brain characteristics in patients with Cushing’s disease revealed that patients with active disease demonstrated smaller hippocampal volumes, more cerebral atrophy, smaller volumes of the bilateral cerebellum, and decreased neurochemical activity in frontal and thalamic areas. Functional MRI in adults with active Cushing’s disease using an emotional faces task demonstrated less activation in the left anterior superior temporal gyrus and higher activation in the frontal, medial, and subcortical regions during the identification of emotional faces. Longitudinal studies demonstrated that after correction of hypercortisolism, hippocampal volumes and neuronal activity increased, and brain atrophy regressed. Cross-sectional studies in patients with long-term remission of Cushing’s disease, showed no differences in hippocampal volumes between patients and healthy matched controls, however cortical grey matter volumes were smaller, and the cortical thickness was found to be decreased. Neurochemical alterations were also found in patients with long-term remission. Furthermore, associations were found between alterations in the brain and clinical and laboratory characteristics (e.g. duration of hypercortisolism, plasma cortisol, urinary free cortisol), as well as associations between structural and functional brain abnormalities and behavioural outcomes, especially in memory and mood domains (Functional status) (Chapter 2). In a study of our department it was demonstrated that patients with long-term remission of Cushing’s disease, when compared to matched healthy controls, demonstrated smaller grey matter volumes in areas in the anterior cingulate cortex, and larger grey matter volumes in the left posterior lobe of the cerebellum in the presence of more depressive symptoms, anxiety, social phobia, apathy and cognitive failure. However, no associations were found between brain alterations and psychological morbidity (Chapter 3). A functional MRI analysis in the same cohort of patients revealed that these patients demonstrated hypoactivation of the ventromedial prefrontal cortex during processing of facial expressions (vs. scrambled faces), without alterations in amygdala activation. Post-hoc analyses revealed decreased functional coupling between the ventromedial prefrontal cortex and the posterior cingulate cortex. Similar to what was observed in chapter 3, no associations were found between brain activation and psychological morbidity (Chapter 4). For an explanation of the potential mechanisms that underlie these alterations in specific brain areas, we presently examine if, and to what extent MR and GR co-localize with other receptors which enable to identify signalling pathways and functionally coordinated regions (2).

Currently, the literature about brain characteristics in patients with long-term remission of Cushing’s disease has been extended. In the same cohort of patients described in chapter 3 and 4, we found widespread reductions in white matter integrity though the whole brain. Interestingly, severity of depressive symptoms correlated with reductions in white matter integrity in the left uncinate fasciculus i.e. a white matter bundle connecting the limbic system with the frontal regions and also known to be an important connection in networks for emotional regulation and stress (3). In addition, patients with long-term remission of Cushing’s disease showed increased resting-state functional connectivity between the limbic network
and the subgenual subregion of the anterior cingulate cortex which is an important target side for negative feedback effects of glucocorticoids and stress-induced HPA-axis activity (4). These findings together with the results reported in chapter 2-4 suggest that previous exposure to hypercortisolism results in long-standing or even irreversible changes in the brain. It should be acknowledged that Cushing’s disease is associated with pituitary deficiencies and multisystem morbidity, which all can affect the brain. For instance, a recent study demonstrated that patients with remission of Cushing’s disease had a higher degree of white matter lesions than controls and patients with active Cushing’s disease, and that the severity of white matter lesions correlated with diastolic blood pressure and duration of hypertension (5), suggesting that the persisting comorbid increased cardiovascular risk also contributes to brain abnormalities. It is tempting to speculate that the observed brain alterations found in patients in remission of Cushing’s disease could, at least in part, explain the psychological morbidity (Symptom status) and subtle cognitive impairments (Functional status). Finally, it is plausible to assume that this specific vulnerability of specific brain regions also applies for patients treated with exogenous glucocorticoids (6).

In Chapter 5 a new tool to measure long-term cortisol was used and evaluated in patients treated for adrenal insufficiency, i.e. measuring cortisol levels in scalp hair. It was observed that patients with hydrocortisone replacement therapy for adrenal insufficiency showed higher hair cortisol levels than both patients with pituitary disease without adrenal insufficiency and healthy controls. Furthermore, male patients with adrenal insufficiency demonstrated higher hair cortisol levels compared to female patients with adrenal insufficiency while using the same hydrocortisone dose. In male patients higher hair cortisol levels were associated with higher BMI (Symptom status). Next, in the same cohort of patients we explored whether systemic cortisol exposure as measured in hair cortisol is reflected by QoL (Chapter 6). It was revealed that patients reported more impairments in QoL compared to healthy controls. A higher daily hydrocortisone intake was associated with more impairment in QoL, but only a few correlations were found for hair cortisol levels, suggesting that QoL impairments in patients with adrenal insufficiency are not per se due to higher cortisol exposure related to replacement therapy.

**Symptom status**

When changes in biological and physiological variables occur, an individual might perceive symptoms. Symptom status is defined by Wilson and Cleary as a patient’s perception of an abnormal physical, emotional, or cognitive state (1). As described in the introduction (Chapter 1) patients with pituitary disease can suffer from profound symptoms, which may persist even after long-term remission. General examples of symptoms reported by patients with pituitary disease are mood swings, pain, visual symptoms, fatigue, joint complaints, weight gain, menstrual problems in females, and erectile dysfunction in men. In the present thesis the examination of symptom status focussed on psychological symptoms in patients with
adrenal insufficiency. Moreover, during the focus group conversations somatic and psychological symptoms were explored.

In Chapter 8, psychological morbidity was examined in patients with adrenal insufficiency treated with hydrocortisone replacement therapy. It could be observed that patients with adrenal insufficiency in a stable medical condition reported more irritability and somatic arousal compared to healthy controls. Similar to the results of chapter 6, hydrocortisone intake was associated with the prevalence of psychological morbidity. In Chapter 11 focus group conversations were described in patients with pituitary disease (i.e. Cushing’s disease, acromegaly, prolactinoma, NFA). The most profound symptom perceived by patients was fatigue. Other examples were pain, visual problems, sleeping problems, changes in physical appearance, physical sexual dysfunction, depressive symptoms, melancholy, mood swings, and anxiety.

**Functional status**

The symptoms patients perceive largely determine whether patients perceive issues in their functioning. Functional status refers to the ability of the patient to perform particular defined tasks.

In the present thesis functional status was examined by the assessment of cognitive functioning in patients with adrenal insufficiency. During the focus group conversations patients also mentioned perceived issues in several functional domains.

Regarding cognitive functioning, it was observed that patients with adrenal insufficiency on long-term hydrocortisone replacement therapy performed worse on memory and executive functioning tasks compared to healthy matched controls. When patients with regular morning hydrocortisone intake were compared with patients that postponed their hydrocortisone morning intake leading to lower cortisol levels (Biological and Physiological variables), we did not observe any immediate deterioration in cognitive functioning. Furthermore, psychological morbidity was associated with more problems with visual memory and executive functioning (Chapter 5). Problems in cognitive functioning were also reported in patients with pituitary disease during the focus group conversations (Chapter 11). Furthermore, impairments were mentioned in physical-, sexual-, psychological- and social functioning. For example, patients reported to feel insecure in social situations and to experience difficulties is social contacts.

**General health perceptions**

General health perceptions integrate all of the preceding concepts, as well as others such as mental health. It refers to a patient’s general perception of his/her current health. Although detailed perceptions of patients of overall well-being were assessed during the focus group conversations, their general health perceptions were less extensively examined. A frequently used manner to assess a patient’s general health perception is by using a visual analogue scale
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(VAS) ranging from 0 to 100 (or 0 to 10) and ask the patient to rate his/her general health. The EQ-5D questionnaire includes such a VAS (7) and was assessed in patients with adrenal insufficiency during the study described in Chapter 8. Patients with adrenal insufficiency on long-term hydrocortisone replacement therapy reported a worse perceived health status compared to matched healthy controls. Worse perceived health status was also observed in patients with pituitary disease (i.e. NFA) (8).

Overall quality of life

Following the Wilson-Cleary model overall QoL integrates all of the preceding concepts, with the influence of characteristics of the patient and the environment. As previously mentioned, QoL should be formulated from the patient perspective. In patients with pituitary disease QoL is commonly evaluated by the use of validated questionnaires, but qualitative methods (e.g. focus group conversations, interviews, drawings) can be used to further elaborate the patient perspective.

A review of the available QoL literature in patients with pituitary disease revealed the negative impact of pituitary disease on QoL, with patients with acromegaly or Cushing’s disease generally demonstrating the greatest impairment in QoL. A relatively small number of studies evaluated interventions aiming to improve QoL, predominantly examining pharmacological and surgical interventions. The number of studies examining QoL in treatment naïve patients was limited, and only a few studies evaluated QoL in patients during long-term follow-up. The cause of the persistent impairment in QoL seems to be multifactorial, since a variety of somatic, psychological and environmental factors has been identified to influence QoL (Chapter 9). Furthermore, the case-control study described in Chapter 6 demonstrated that patients with adrenal insufficiency treated with hydrocortisone replacement therapy reported worse QoL compared to matched healthy controls.

Although the majority of the studies on QoL and QoL-related factors used quantitative methods (i.e. questionnaires), only a very few used qualitative methods (i.e. interviews, focus group conversations), despite that qualitative methods allow to extensively explore the patient perspective. Therefore, in Chapter 11 focus group conversations were used to define patient perceived QoL, and also to identify factors they perceive to contribute to QoL. Issues emerged that are not currently included in available disease-specific questionnaires i.e. visual limitations, issues with a desire to have children/family planning, fear of collapsing, fear of recurrence, panic, persisting thoughts, problems with an altered personality, anger, jealousy, sadness, frustration, difficulties in communicating about the disease, lack of sympathy and understanding by others, and a reduced social network. Factors that may contribute to a decreased QoL were less effective coping strategies, negative illness perceptions, negative beliefs about medicines (Characteristics of the patient), and unmet needs regarding care (Characteristics of the patient and the environment).
Individual and environmental characteristics

Individual characteristics (or patient characteristics) as formulated in the Wilson-Cleary model cover factors such as personality, motivation, values, and preferences. Patients’ preferences or values refer to the value patients attach to a particular consequence of a disease. For instance, a particular symptom can be more burdensome to a patient, while the same symptom is not for another patient. Illness perceptions and beliefs about medication as formulated by the extended Common-Sense Model of Self-Regulation (CSM) can be categorised into values and preference in the Wilson-Cleary model. These preferences and values play an important role at several points of the Wilson-Cleary model and are particular important in understanding general health perceptions and overall QoL, which is in accordance with the extended CSM, since this model also states that illness perceptions and beliefs about medication correlate with QoL (Chapter 1, Figure 3).

Because the majority of the patients with pituitary disease may need lifelong medical treatment and in keeping with the theory of the extended CSM (see chapter 1), we assessed illness perceptions and beliefs about medicines in patients with acromegaly in Chapter 10. This study demonstrated that stronger beliefs about the necessity of somatostatin analogs were associated with attributing more symptoms to acromegaly, perceiving more negative consequences, and lower disease-specific QoL. More concerns about the perceived side-effects of somatostatin analogs were associated with perceiving more variability in symptoms. During the focus group conversations (Chapter 11) patients also reported negative illness perceptions, such as the chronic time course of their disease, and they reported concerns about potential side effects of their medication. In accordance, negative illness perceptions in patients with Cushing’s disease or acromegaly were previously reported in a quantitative study (9;10). Furthermore, less efficient coping strategies were reported in the focus group conversations, such as withdrawal and overdoing activities. These less efficient coping strategies were also previously observed in a quantitative study (11). A recent study in patients with Cushing’s disease demonstrated that these less efficient coping strategies were associated with more impairment in QoL (12).

Another characteristic of the patient is the personality. Personality traits were assessed in Chapter 6 in patients with adrenal insufficiency on long-term stable hormone replacement. In this study, we did not find any differences in personality traits between patients and healthy matched controls. Although these results suggest that personality traits are less sensitive to pituitary/adrenal dysfunctions (in contrast to psychological functioning), it is intriguing that maladaptive personality traits have been observed in patients with long-term remission of Cushing’s disease (13;14), acromegaly (15;16), prolactinoma (17), and to some extent in NFA(16). Therefore, one might speculate that it is more likely that the observed maladaptive personality traits seen in patients with a functional pituitary adenoma are related to the (previous) exposure to excessive hormone levels, since the maladaptive personality traits were not observed in patients with primary adrenal insufficiency.
Environmental characteristics may underlie factors such as economical-, psychological-, and social support, with the last two playing an important role at General Health perception and Overall Quality of Life.

During the focus group conversations patients reported unmet needs regarding care, such as insufficient information and no recognition for certain complaints. These unmet needs can be categorized under patient characteristics, since they can be influenced by personal factors. On the other hand, unmet needs can also be influenced by environmental characteristics (e.g. availability of healthcare facilities). For example, patients reported dissatisfaction with other aspects of medical care i.e. stress-management training, lifestyle recommendations, physiotherapists, dietitians, medical sports experts and psychologists. These unmet needs can be caused by limitations in economical supports or inadequate referral of a patient to healthcare professionals in other medical disciplines. It should also be acknowledged that some types of support (e.g. psychological-, social support) are less well developed for a specific disease as pituitary disease. Besides professional environmental factors (i.e. healthcare facilities), there are also personal environmental factors. The most important person in a patient’s social network is most of the time the spouse or partner. Therefore, the perspective of the partner was also elucidated by the use of focus group conversations (Chapter 12). Partners reported worries related to the pituitary disease and negative beliefs about medication, coping challenges, relationship issues, social issues, and unmet needs regarding care. These observations clearly demonstrate that chronic care for patients with pituitary disease is not limited to the patient alone.

Based on the focus group conversations with patients (chapter 11), a disease-specific patient reported outcome measure (PROM) was developed. This measure assesses to which extent patients are bothered by certain complaints, as well as their needs for support from healthcare professionals, and was named the Leiden Bother and Needs Questionnaire for Pituitary disease (LBNQ-Pituitary). The final LBNQ-Pituitary consists of 26 items covering 5 subscales i.e. mood problems, negative illness perceptions, issues in sexual functioning, physical and cognitive complaints, issues in social functioning. These subscales were found to be reliable, and their validity was established by significant correlations between the LBNQ-Pituitary and other validated measures (Chapter 13). This questionnaire can be helpful in addressing the unmet needs experienced by patients.

Finally, a SMI was developed for patients with pituitary disease and their potential partners i.e. Patient and Partner Education Programme for pituitary disease (PPEP-Pituitary). This SMI was aimed to (at least partly) fulfill the unmet needs regarding support for psychological and social issues. PPEP-Pituitary was based on the standardized Patient and Partner Education Programme initially developed for patients (and partners) with Parkinson’s disease (18). A multicenter randomized-controlled trial revealed that patients reported more self-efficacy after PPEP-Pituitary which persisted after 6 months. Furthermore, patients reported less bother by mood problems directly after PPEP-Pituitary, however this returned to baseline
levels after 6 months follow-up. Partners reported more vitality, less depressive symptoms and more treatment control after PPEP-Pituitary which persisted to after 6 months (Chapter 14).

**Future research perspectives**

With the studies described in this thesis we aimed to provide an overview of health outcomes in persons with pituitary disease following the concepts of the Wilson-Cleary model. Although this shows health outcomes in each concept of the model, the performed studies are only a start of the full picture. For instance, there might be differences between the different pituitary/adrenal diseases, and the health outcomes are not elaborated for each disease. For example, (f)MRI studies were performed in patients with long-term remission of Cushing’s disease, but considering the present observations in patients with adrenal insufficiency, it would also be interesting to investigate whether, possibly similar underlying biological variables might also explain the impairments seen in patients with adrenal insufficiency. This would be very intriguing to investigate, because the actions of glucocorticoids in the brain appear to follow an u-shaped dose response curve (19). Furthermore, more prospective QoL studies with long-term follow-up including treatment naïve patients are needed to provide better insight into the time course of QoL and potential modifiers. An increased awareness of patients' needs for support would facilitate the translation from patients' needs to optimal patients’ care. The reported unmet needs described in chapter 11 exemplify that it is plausible to assume that paying more attention to patients' needs for support will most likely positively affect QoL, but of course, this should be investigated in future studies (Figure 1). Finally, the randomized, controlled trial (PPEP-Pituitary) aiming at intervening at the level of patient- and environmental characteristics, demonstrated both an increased self-efficacy in patients and better QoL in their partners. For the next steps the aim is to evaluate PPEP-pituitary in a clinical setting with one or two additional refreshing/booster sessions after 6 months-12 months.

**Clinical implications of the Wilson-Cleary model**

The studies described in this thesis emphasize that although patients may be in a stable medical condition, health issues are present at each level of the Wilson-Cleary model. By applying the Wilson-Cleary model to patients with pituitary disease, it can be observed that persistent impairments in QoL in these patients might be explained by issues at each stage of this model. This also provides some insight into the variety in clinical outcome with some patients facing severe problems, while others are not or only slightly affected. It emphasises that improvement in overall QoL in patients with pituitary disease needs optimal biomedical treatment initiating a cascade of improvement in health outcomes starting with a better symptom status. Further improvement of QoL should be supported by a pituitary specific care trajectory, including PPEP-Pituitary, in order to beneficially affect characteristics of the
patient and the (healthcare) environment, with the ultimate goal to optimize QoL in patients with long-term remission of pituitary disease.

REFERENCES


