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Title: Understanding clinical outcome in patients with pituitary disease: a biopsychosocial approach
Issue Date: 2017-09-28
CHAPTER 1

General introduction & outline of the thesis
INTRODUCTION

Pituitary adenomas are benign tumours of the pituitary gland. The estimated prevalence of pituitary adenomas is 78 to 94 cases per 100,000 individuals, with an incidence of four cases per 100,000 individuals (1). These rare, usually slow growing adenomas can be either functional e.g. hormone producing resulting in excessive endocrine activity and classical endocrine syndromes, or non-functional e.g. non-hormone producing resulting in clinical symptoms only in case of significant mass effects. Furthermore, they can be categorized into microadenomas (< 1 cm) and macroadenomas (> 1 cm). Pituitary adenomas can be treated by transsphenoidal surgery, additional radiotherapy or medical treatment and sometimes an expectative approach. The local mass effect of the tumour and/or the treatment can result in pituitary insufficiency, i.e. hypopituitarism, which can be treated by hormone replacement therapy (2). However, despite optimal medical treatment several physical, psychological and social complaints may persist, despite long-term remission (3). This chapter provides an overview of the functioning of the hypothalamic-pituitary axes and the consequences of defects in this system, in particular the effect of dysfunctions of the pituitary-adrenal axis on the central nervous system. Furthermore, the challenges related to these dysfunctions and the long-term clinical outcomes are discussed. Given the biopsychosocial approach adopted in this thesis, psychological and social aspects are described in detail including illness perceptions, beliefs about medicine, quality of life, as well as self-management approaches for dealing with chronic illness directed to improve patient well-being.

Hypothalamic-pituitary axes

The functional links between the hypothalamus, the pituitary, and related endocrine glands are known as the hypothalamic-pituitary-end organ axes. The hypothalamus secretes releasing hormones, i.e. corticotropin-releasing hormone (CRH), growth hormone releasing hormone (GHRH), thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH), and inhibitory hormones, i.e. somatostatin and dopamine. In addition to the hypothalamus playing a role in the neuroendocrine system, it is also involved in the regulation of body temperature, thirst, appetite and sleep (2).

The pituitary gland lies at the base of the skull in a cavity of the sphenoid bone, also known as the hypophysial fossa which is a part of the sella turcica (4). The pituitary is connected to the hypothalamus by the pituitary stalk, and consists of a posterior lobe and an anterior lobe. The posterior lobe secretes:

- Vasopressin (also known as anti-diuretic hormone (ADH)) is the key regulator of sodium and water balance and plays a role in cardiovascular function;
- Oxytocin has a role in the contraction of smooth muscles.

The anterior lobe of the pituitary is stimulated by the releasing hormones secreted by the hypothalamus in order to secrete the following hormones (2):
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- Adrenocorticotropic hormone (ACTH) targets the adrenal cortex to secrete cortisol;
- Growth hormone (GH) acts mainly on the liver to produce insulin-like growth factor-1 (IGF-1) which stimulates growth of bone and muscle. GH also has a direct effect on tissues stimulating growth;
- Prolactin which acts on breast tissue and stimulates lactation;
- Thyroid-stimulating hormone (TSH) stimulates the thyroid gland to produce thyroid hormones ($T_3$ and $T_4$);
- Follicle-stimulating hormone (FSH) and luteinising hormone (LH) act on the gonadal glands to regulate the secretion of testosterone in males, and oestrogen and progesterone in females.

Under normal conditions the hypothalamic-pituitary axes are highly regulated. However, dysfunctions can occur at the level of the end organ (primary disorder), at the level of the pituitary (secondary disorder), or at the level of the hypothalamus (tertiary disorder), resulting in dysregulation of the hypothalamic-pituitary axes. In case of a pituitary adenoma, classical syndromes can develop:

**Cushing’s disease**
ACTH secreting pituitary adenomas result in excessive adrenal cortisol, which leads to Cushing’s disease. Clinical features of Cushing’s disease are (central) obesity, rounded face (i.e. moon face), easy bruising, stretch marks, hirsutism (Figure 1), high blood pressure, diabetes mellitus, irregular menstrual periods in women, erectile dysfunction in men, easy fractures of bones, muscle weakness, acne, poor wound healing, infections and psychological disturbances (e.g. psychosis, depression). Cushing’s disease is treated by removal of the pituitary adenoma by transsphenoidal surgery. Several approaches can be used in case of residual adenoma, i.e. reoperation, conventional radiotherapy or bilateral adrenalectomy. Blockers of steroidogenesis, i.e. metyrapone and ketoconazole are available for (temporary) reduction of cortisol secretion. New medical therapies are emerging including treatment with a somatostatin analogs with a high affinity for the somatostatin receptor subtype 5 (i.e. Pasireotide), a glucocorticoid receptor blocker (i.e. Mifepristone), and a new generation steroid synthesis inhibitors (5). Since hypercortisolism is a lethal condition, removal of both adrenals (bilateral adrenalectomy) is a viable option to establish cure of hypercortisolism, when surgery and radiotherapy have not led to the desired outcome (2;6). Although physical and psychological symptoms improve after correction for hypercortisolism, persistent morbidity is often observed in patients with long-term remission of Cushing’s disease, such as increased cardiovascular morbidity, osteoporosis (7), impairments in cognitive functioning (8;9), psychopathology (10) and increased mortality (9).
Acromegaly
GH producing pituitary adenomas result in exposure to elevated GH and IGF-I levels. Excessive GH levels during childhood or adolescence will lead to gigantism, while elevated GH levels during adulthood will lead to the classical syndrome of acromegaly. Clinical manifestations of acromegaly include changes in appearance including soft tissue overgrowth with increased size of hands and feet, and coarsening of facial features (Figure 2), deepening of voice, visual field defects, headaches, excessive sweating, weight gain, oiliness of the skin, fatigue, joint pain, menstrual disorders, erectile dysfunction in men, and decreased libido. Other symptoms frequently seen in patients with acromegaly are sleep apnoea syndrome, carpal tunnel syndrome, athropathy, diabetes mellitus, colonic polyps, and heart failure. Acromegaly is usually treated by removal of the pituitary adenoma by transsphenoidal surgery, which can be curative when the adenoma is not invasive, or by medical treatment with somatostatin analogs (i.e. Octreotide) or a GH receptor antagonist (i.e. Pegvisomant). Treatment
with somatostatin analogs consists of (lifelong) monthly subcutaneous or intramuscular injections of sustained-release somatostatin analogs (i.e. Octreotide LAR or lanreotide) and pegvisomant consists of daily injections. Also a combination therapy with pegvisomant and somatostatin analogs can be used. Most frequently reported side effects (>10%) of somatostatin analogs are gastrointestinal complaints, headache, cholelithiasis, and hyperglycemia (12). Conventional radiotherapy is one of the alternative treatment options (2;6).

Although symptoms improve after normalisation of GH and IGF-I levels, long-term morbidity in patients with biochemically cured acromegaly is seen, characterized by joint complaints, hypertension, myocardial infarction, diabetes mellitus (13), psychopathology (14), and increased mortality (15).

Figure 2. Signs in acromegaly, derived from Levy & Howlett (6).

Prolactinoma
Prolactin secreting pituitary adenomas are named prolactinomas and are the most common pituitary adenomas, with 60% of all pituitary adenomas being a prolactinoma. Clinical fea-
tures of prolactinomas are galactorrhea, amenorrhea or oligomenorrhea in women, erectile dysfunction in men, decreased libido, and subfertility \(2,6\). Prolactinomas are treated by medical therapy with dopamine agonists (e.g. Cabergoline) which consists of an orally taken dose once or twice a week. Most frequently reported side effects (>10%) are headache, dizziness, dyspepsia, gastritis, nausea, stomach ache, asthenia, and fatigue \(16\). Transsphenoidal surgery is a good alternative in case of side effects or resistance to the therapy. Conventional radiotherapy is reserved for patients who have persistent hyperprolactinemia after surgery or medical treatment \(2,6\).

**Non-functioning pituitary adenoma**

Non-functioning pituitary adenomas (NFAs) are named as such because they do not secrete any hormones, consequently they are usually large when the diagnosis is established. The mass effects of the adenoma can result in pressure on the pituitary itself or to adjacent structures, such as the optic nerve or optic chiasm. Clinical features of NFAs are visual field defects, hypopituitarism and headache. Since these adenomas are generally large, transsphenoidal surgical resection is usually required to relieve mass effects. Conventional radiotherapy may be used to reduce tumour progression or recurrence of the tumour \(2\). Even after long-term remission of NFA, patients may suffer from persistent visual field defects \(17\).

**Hypopituitarism**

For all pituitary adenomas counts that due to damage to the pituitary as a result of the mass effect of the tumour, the surgical treatment or the radiotherapy, it could be that one or more pituitary hormones are not (or not sufficiently) produced. This is known as hypopituitarism. The majority of the patients with hypopituitarism need lifelong treatment with hormone replacement therapy (Table 1), aiming to mimic the physiology of end organ hormones. Replacement therapy for adrenal insufficiency is of particular relevance, since too low cortisol levels can lead to an acute adrenal crisis (i.e. Addison’s crisis) which is a life threatening situation. On the other hand, when replacement therapy consists of too high hydrocortisone dosages this may lead to exposure to hypercortisolism resulting into symptoms similar to Cushing’s disease. Furthermore, replacement dose adjustments are required in stressful situations, i.e. physical and psychological stressors or illness. Considering these serious effects, adequate replacement therapy in adrenal insufficiency as well as, adaptation of the dose during stress, is crucial \(18\).

Adrenal insufficiency can be caused by an ACTH insufficiency due to damage to the pituitary, also known as secondary adrenal insufficiency (SAI), it can also be the result of damage to the adrenal glands, known as primary adrenal insufficiency (PAI) or Addison’s disease. PAI is most frequently caused by auto-immunity or following bilateral adrenalectomy after for instance a persisting Cushing’s disease.
Table 1. Hormone replacement therapy in case of hypopituitarism

<table>
<thead>
<tr>
<th>Insufficiency of</th>
<th>Replacement therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>Hydrocortisone: 15-40 mg per day divided into two to three doses</td>
</tr>
<tr>
<td>Thyroid hormones</td>
<td>Levothyroxine: 1.6 µg/kg per day (100-200 µg usually adequate)</td>
</tr>
<tr>
<td>Gonadotropic hormones</td>
<td>Adrogel: 50-100 mg per day (males)</td>
</tr>
<tr>
<td></td>
<td>Combination estrogen/progestin (females)</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Growth hormone: 2-5 µg/kg per day</td>
</tr>
</tbody>
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**Titration of the hydrocortisone dose**

Hydrocortisone replacement therapy needs to be balanced between over- and underreplacement. It aims at achieving the normal circadian rhythm of cortisol secretion, with high cortisol levels in the morning and lower cortisol levels in the afternoon and evening. Furthermore, it is recommended that hydrocortisone intake should be individualized, since it is likely that there is large individual variation in hydrocortisone requirements taking into consideration differences in cortisol sensitivity due to polymorphisms of the glucocorticoid receptor gene (19). For the determination of the required individual hydrocortisone dosage it is advocated to take into account blood pressure, metabolic derangements and patient perceived sense of well-being (20). Furthermore, clinicians can rely on cortisol levels as measured in saliva, serum and plasma. However, limitations of these measurements are that cortisol levels are measured at one time point and that they do not reflect cortisol action at tissue level. Apparently, a recently developed method enables to retrospectively assess cortisol levels for longer time periods, namely the assessment of cortisol in scalp hair (21). Scalp hair grows with one cm per month (22), so a hair sample of for example the proximal three cm represents the cortisol concentration of the last three months.

**Long-term effects of cortisol on the central nervous system**

It postulated that the causes for persistent morbidity in patients with dysfunctions of the pituitary-adrenal axis are multi-factorial, including imperfections of surgical treatment of the pituitary gland or intrinsic imperfections in hormone replacement therapy. Furthermore, patients who are previously exposed to hypercortisolism, such as in Cushing’s disease, may also suffer from potential irreversible effects of the cortisol excess on the central nervous system and peripheral tissue.

In the human brain, the effect of cortisol is mediated via two types of receptors: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). MR is highly expressed in the hippocampus, a brain structure involved in memory and learning processes, while GR is widely expressed throughout the whole brain. Cortisol has a tenfold higher binding affinity for the MR than for the GR. Consequently, MRs are activated first when cortisol levels increase, followed by GRs activation when cortisol levels increase further (23).
The negative effects of cortisol excess on the central nervous system are well-recognized in animal brains, but less well established in the human brain. In 1992 Starkman and colleagues were the first to report on hippocampal volumes obtained from routine pituitary magnetic resonance imaging (MRI) diagnostics of patients with active Cushing’s disease, and compared these with healthy control data derived from the literature. It was observed that hippocampal volume was decreased during active Cushing’s disease (24), but a partial recovery was observed after successful biomedical treatment (25;26). The field of neuroimaging has been rapidly expanding and currently available neuroimaging techniques enable a more precise evaluation of the brain. Besides the evaluation of brain structures, also brain function can be currently examined i.e. functional MRI (fMRI). fMRI is based on the assumption that when a brain region is active more oxygen is needed and therefore a higher blood flow is achieved. By measuring changes in oxygen consumption during processing of a task, it can be inferred what areas are activated during a particular task (27). The currently available neuroimaging techniques can be used to provide more (new) insight into brain characteristics of patients exposed to hypercortisolism such as in Cushing’s disease.

Quality of Life
In clinical studies the umbrella term ‘patient reported outcome’ (PRO) is frequently used, referring to a measure of a patient’s health status directly derived from the patient, without interpretation of clinicians or anyone else (28). Thereby, the term PRO indicates the importance of the patient’s own perspective on their health status. ‘Quality of life’ (QoL) can be seen as one type of PRO.

Although it is established that QoL should cover physical-, psychological-, and social well-being (in accordance with the biopsychosocial model) (29), one concrete definition of QoL is lacking, which poses major challenges for the evaluation and interpretation of QoL (30). A model that is frequently used to conceptualise QoL and whose validity is supported by empirical evidence over the years (31) and has been widely applied to different patient populations (32-34) is the conceptual model proposed by Wilson and Cleary (1995) (35). This model establishes the biopsychosocial model (29) by integrating the clinical paradigm i.e. the biomedical paradigm and the quality of life model (i.e. social science paradigm). Where the biomedical paradigm focusses on pathological processes, and biological, physiological, and clinical outcomes, the social science paradigm focusses on dimensions of functioning and overall well-being. This model states that health can be thought of as a continuum of increasing biological, psychological and social complexity, with on the one hand pure biological measures, and on the other measures of general health perceptions (Figure 3). It explicates the proposed dominant causal relationships (bold) and mediating factors. From left to right, it goes from cell-level to the individual to the interaction of the individual in its social context. The arrows used in figure 3 do not imply that there are no reciprocal relations, just as the absence of arrows does not imply that there are no such relationships. Furthermore, it should be
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noted that the relation between symptom status and biological and physiological variables is rather complex. In other words biological and physiological variables can be profoundly abnormal without the patient perceiving symptoms, or the other way around with the patient perceiving profound symptoms for which no biological or physiological abnormalities can be identified.

**Figure 3.** Wilson-Cleary model of QoL (35).

**Biological and Physiological variables:** function of cell, organs, and organ systems e.g., diagnoses, laboratory values, measures of physiological function, and physical examination findings.

**Symptom status:** a patient’s perception of an abnormal physical, emotional or cognitive state.

**Functional status:** ability of the individual to perform particular tasks. The main domains of functioning are physical functioning, social functioning, role function, and psychological functioning.

**General Health perceptions:** subjective rating of health, and represents and integrates all of the previous health concepts.

**Quality of life in pituitary disease**

In patients with pituitary disease QoL is traditionally assessed by the use of questionnaires. QoL can be assessed by validated questionnaires and it is usually recommended that a generic questionnaire (assesses general QoL domains, valid for healthy respondents or patients with any medical condition) is combined with a disease-specific questionnaire (assesses QoL aspects relevant to a specific disease), in order to assess both the general perspective of QoL and disease-specific aspects (36). Disease-specific QoL questionnaires for patients with pituitary disease have been developed e.g. the ACROQoL for acromegaly (37-39), the QoL-AGHDA for growth hormone deficiency (GHD) (40), and the Tuebingen CD-25 and the CushingQoL for Cushing’s disease (41-43). Unfortunately, no questionnaires are available for patients with a non-functioning pituitary adenoma or a prolactinoma. Due to the large variety of used
QoL questionnaires (e.g. generic, disease-specific questionnaires) it is difficult to compare QoL between studies. However, in general it can be observed that patients with pituitary disease report impairments in QoL during active disease, which improves somewhat after surgery (44), medical treatment (i.e. somatostatine analogs, GH receptor antagonists in acromegaly or a glucocorticoid receptor blocker in Cushing’s disease) (45-47) or growth hormone replacement therapy (48). However, QoL evaluations after long-term remission demonstrate persistent impairments in QoL. For example, patients report musculoskeletal pain (49), sexual dysfunction (50), worse mental health (51), and fatigue (52). Furthermore, disease-specific differences were observed between various pituitary diseases, with patients with acromegaly reporting impairment characterized by worse physical performance and bodily pain (3), and patients with Cushing’s disease reporting impairment characterized by worse psychological well-being and psychological and social adjustment (53). Unfortunately, prospective QoL studies with long-term follow-up including treatment naïve patients are lacking resulting a lack of insight into the time course of QoL impairments, as well as the effectiveness of treatment in terms of QoL.

**Illness perceptions and beliefs about medicine**

Illness perceptions are conceptualized in the Common-Sense Model of Self-Regulation (CSM) (54). This model views the patient as an active problem solver who makes sense of his/her illness. It also conceptualizes how patients develop emotional and cognitive representations of their illness and how they develop coping strategies to manage their illness e.g. self-management behaviour. Three stages are specified in this model (Figure 4). First, patients develop illness perceptions in response to stimuli, i.e. information from the social environment such as friends, family, medical doctors and (social) media, but also information derived from previous or current experience with illness. Both emotional illness perceptions (e.g., anxiety, anger) and cognitive illness perceptions are formed. These cognitive illness perceptions can be organized around five content domains:

- **Identity**: the label that is used to describe the condition and the associated symptoms;
- **Cause**: the perceived cause of the illness;
- **Timeline**: the expected duration of the illness;
- **Consequences**: the perceived effect of the illness on physical, psychological, and social well-being;
- **Cure/control**: the perceived extent to which the illness can be controlled or cured through treatment and behaviour.

Illness perceptions then influence the coping strategies patients use to manage their illness and their emotional well-being. The used coping strategies will influence outcome. Finally, the patient appraises the used coping strategies and outcomes, and decides to continue with the same strategy or to adapt their coping behaviour. A central aspect of this model is the assumption that emotional and cognitive responses are processed in parallel. Furthermore,
the presence of a feedback loop illustrates the self-regulation process, in which individuals use coping strategies, appraise progress and adapt coping strategies when needed (55). In patients with pituitary disease it was demonstrated that these patients reported more negative illness perceptions compared to patients with acute and chronic conditions. For instance, it was demonstrated that patients with Cushing’s disease or acromegaly perceived more negative consequences of the disease compared to patients with acute pain and they perceived less personal control than patients with chronic obstructive pulmonary disease (56;57). Furthermore, patients reported to use less effective coping strategies, including performing less active coping, seeking less social support, and using more avoidant coping strategies compared to an a-select sample of the Dutch population (58).

Patients not only have certain perceptions about their illness, they also have certain beliefs about their treatment i.e. beliefs about medicine. These beliefs can be categorized into beliefs about the necessity of taking medication and concerns about negative effects of medication. Similar to illness perceptions as conceptualized in the CSM, beliefs about medicines also contain emotional and cognitive aspects which are processed in parallel. Therefore, it can be postulated that beliefs about medicine can be incorporated into the CSM (Figure 4) (59), resulting in the extended CSM in which beliefs about medicine are related to illness perceptions and to coping strategies. Previous research already provided evidence for the existence of these associations in patients with other chronic conditions (60;61).

![Diagram](image)

**Figure 4.** The Common-Sense Model of Self-Regulation (black) extended with beliefs about medicine (grey). Adapted from Horne (59).

**Self-management**

For several chronic diseases self-management interventions (SMIs) have been developed aiming to improve well-being of patients (62). Self-management is defined by Barlow et al.
(2002) as “the individual’s ability to manage the symptoms, treatment, physical, psychological, and social consequences and life style changes inherent in living with a chronic condition. Efficacious self-management encompasses ability to monitor one’s condition and to effect the cognitive, behavioural and emotional responses necessary to maintain a satisfactory quality of life” (63). This definition further stresses the importance of psychological and social management, besides the management of medical treatment. Between existing SMIs great diversity in composition exists which can be explained by the fact that SMIs may be based on different theoretical models (e.g. the CSM), but also to differences between diseases, as well as differences in self-management aims. For instance, SMIs can focus on managing medication intake, lifestyle changes, or managing emotional aspects of having a chronic disease. Nevertheless, widely used components in SMIs are:

• Information provision;
• Self-monitoring: systematic recording of information (e.g. symptoms) to increase awareness and recognise potential patterns;
• Skills training: illness-related skills (e.g. adjusting medication in response to symptoms);
• Behaviour change: adopting new behaviours and/or changing pre-existing behaviours;
• Changing unhelpful beliefs (e.g. beliefs about themselves, self-efficacy beliefs, illness perceptions, beliefs about medicine);
• Managing emotions: e.g. stress management, training in coping strategies, managing anxiety and depressive symptoms;
• Enhancing communication skills and social support: supportive environment of the self-management group, enhancing communication and support by relatives, friends, family, but also health care professionals (64).

An example of a SMI which includes these components is the Patient and Partner Education Programme for patients with Parkinson’s disease (65). This programme comprises techniques from cognitive behavioural therapy, such as cognitive restructuring, systematic relaxation, situational behavioural analysis, and social skills training. The programme consists of eight weekly session of 90 minutes (Figure 5). Although this SMI was originally developed, and found to be effective for patients with Parkinson’s disease (65-67), it has also been adapted and found to be effective for patients with Huntington’s disease (68). Recently, a manual for using this SMI in patients with chronic disease in general (PPEP4ALL) was published (69).

OUTLINE OF THE THESIS

Pituitary adenomas are benign tumours of the pituitary gland. Despite optimal medical treatment several physical, psychological, and social complaints may persist, even after long-term remission (3). This thesis aims to describe health outcomes in these patients by using a biopsychosocial approach covering the continuum with on the one hand biological and
physiological measures and on the other measures of general health perceptions and QoL as described by the Wilson-Cleary model (Figure 3) (35).

Figure 5. Themes and aims of the patient education programme. Figure derived from A’Campo et al. (66)

In part I biological and physiological variables will be described at the level of the brain (e.g. grey matter, neuronal processing) in patients with long-term remission of Cushing’s disease, as well as whether brain characteristics are associated with patient reported psychological morbidity (Symptom status). Part II will again focus on biological and physiological variables, but this time on long-term cortisol levels measured in scalp hair in patients with adrenal insufficiency treated with replacement therapy. Associations will be assessed between hair cortisol levels and anthropometrics (Symptom status), and QoL. In addition, psychological morbidity (Symptom status) and cognitive functioning (Functional status) will be examined in patients with primary adrenal insufficiency. Finally, in part III QoL in patients with pituitary disease will be discussed based on studies using QoL questionnaires, as well as QoL as formulated by patients during focus group conversations. Furthermore, illness perceptions and beliefs about medication will be examined. In addition, the impact of pituitary disease on the lives of partners will be described (Characteristics of the environment), as well as the
development of a patient reported outcome measure (PROM) to assess whether patients are bothered by complaints and whether they need (specific) support from their environment. Finally, the evaluation of a SMI for patients with pituitary disease and their partners will be described which potentially positively influence characteristics of the environment and characteristics of the patient aiming to improve overall QoL of patients and their partners.

**Part I: Long-term effects of Cushing’s disease on the human brain**
Considering the persistent impairments in psychological and cognitive functioning in patients with long-term remission of Cushing’s disease and the fact that the brain is a major target area for cortisol, the first part of this thesis was aimed to assess whether the persistent impairments might be explained by structural and/or functional alterations in the brain. For this research question, first, an overview is provided of the outcome of (functional) MRI studies of the brain in patients with Cushing’s disease (Chapter 2). Then in Chapter 3 grey matter volumes in patients after long-term remission of Cushing’s disease were examined, as well as whether potential brain alterations were associated with patient reported psychological and cognitive dysfunction, and clinical severity. Besides this structural evaluation, a functional evaluation was performed in the same cohort of patients by measuring brain activation during emotion processing using an emotional faces paradigm (Chapter 4).

**Part II: Clinical implications of adrenal insufficiency**
Part II focusses on patients with adrenal insufficiency treated with hydrocortisone replacement therapy. In these patients replacement therapy is aiming to mimic the circadian rhythm of cortisol secretion. It is recommended that hydrocortisone intake should be individualized and clinicians can currently rely on saliva, serum and plasma which measures cortisol levels at one time point. In Chapter 5 a new tool to measure cortisol levels in patients with adrenal insufficiency was used and evaluated, namely measuring cortisol in scalp hair. For this evaluation hair cortisol levels of patients with adrenal insufficiency treated with replacement therapy were compared with patients with pituitary disease without adrenal insufficiency and healthy controls. Furthermore, associations were examined between hair cortisol levels, hydrocortisone intake and anthropometrics. In the same patient population it was also examined whether long-term cortisol levels as measured in scalp hair were associated with patient reported QoL (Chapter 6).

As previously mentioned, the brain is a major target area for cortisol and therefore it plays an important role in psychological and cognitive functioning. Considering the HPA-axis dysregulation in patients with adrenal insufficiency it can be suggested that their psychological and cognitive functioning is affected. Therefore, in Chapter 7 cognitive functioning was examined in patients with adrenal insufficiency. For this evaluation cognitive functioning of patient with adrenal insufficiency was compared to cognitive functioning of healthy matched controls. Furthermore, we aimed to examine the direct effect of low cortisol levels
on cognitive functioning. Therefore, patients with normal hydrocortisone intake were also compared to patients with postponed hydrocortisone intake. The last chapter of this part describes psychological symptoms and functioning in patients with adrenal insufficiency. Psychological morbidity, personality traits, and QoL in patients with adrenal insufficiency were evaluated by using validated questionnaires. In addition, it was examined whether psychological morbidity, personality traits, and QoL were associated with hydrocortisone intake.

**Part III: The next step in improving quality of life in pituitary disease**

The persistent impairments in QoL seen in patients with pituitary disease might be explained by issues in the preceding domains of the Wilson-Cleary model i.e., biological variables, symptom status, functional status, but they might also be influenced by patient characteristics (e.g. their values and beliefs) and environmental characteristics (e.g. partner, social support), i.e. psychological and social aspects. In order to further elaborate QoL and determinants of QoL in patients with pituitary disease, we first provided an overview of the available QoL studies in patients with pituitary disease (Chapter 9). Considering the fact that the majority of the patients with pituitary disease may need lifelong medical treatment, as well as that illness perceptions and treatment beliefs are potentially influencing factors of self-management behaviour, beliefs about medicine and their relation to illness perceptions and QoL were examined in Chapter 10. The patient perspective of QoL in patients with pituitary disease was further elucidated by the use of focus group conversations. Besides the patient perspective, the perspective of potential partners of patients with pituitary disease was also explored by the use of focus group conversations. The results of these focus group studies were reported in Chapter 11 and Chapter 12. Then, we developed a disease-specific patient reported outcome measure (PROM) in order to assess whether patients are bothered by certain consequences of the disease, as well as whether they need support for these issues i.e., the Leiden Bother and Needs Questionnaire for patients with pituitary disease (LBNQ-Pituitary). The process of development and validation of the LBNQ-Pituitary is described in Chapter 13. Chapter 14 describes how the Patient and Partner Education Programme was adapted for patients with pituitary disease (PPEP-Pituitary) and evaluates the effectiveness of this SMI by using a multi-centre randomized controlled trial.

**REFERENCES**


Chapter 1


Introduction


Chapter 1


