Chapter 1

General Introduction

Contents

1. Introduction

Pituitary adenomas are rare and benign tumors, but can cause serious morbidity due to local mass effects and pituitary insufficiency, and/or due to excessive secretion of pituitary hormones. Pituitary adenomas can be treated by surgery, radiotherapy, and medical therapy. However, despite curative treatment of the adenomas *per se*, multiple physical and psychological complaints may persist, even after long-term remission. The studies described in this thesis focus on the long-term psychological consequences of pituitary adenomas.

2. The neuroendocrine system: an overview

The pituitary gland and hypothalamus form a functional unit. The hypothalamus relays endocrine and neural signals to the pituitary which in turn releases hormones that influence most endocrine systems in the body. Together, the hypothalamus and the pituitary exert control over the function of the thyroid gland, the adrenal glands, and the gonads (1).
The hypothalamus is located below the third ventricle and just above the optic chiasm and pituitary gland and links with the central nervous system (2). The hypothalamus secretes important regulating hormones: growth hormone releasing hormone (GHRH), somatostatin, dopamine, thyrotropin releasing hormone (TRH), corticotropin releasing hormone (CRH), and gonadotropin releasing hormone (GnRH). In addition, the hypothalamus is involved in the regulation of other important processes including the regulation of body temperature and food intake (1).
The pituitary is located at the base of the skull in the sella turcica and consists of a posterior (neurohypophysis) and anterior (adenohypophysis) lobe. The posterior lobe secretes two hormones: antidiuretic hormone (ADH) and oxytocin. ADH is an important regulator of water balance and plays a role in cardiovascular function. Oxytocin is a hormone important in for example the contraction of smooth muscles. The anterior lobe of the pituitary is the most richly vascularized tissue of al mammalian tissues and secretes six major hormones (1):

1. Adrenocorticotropic hormone (ACTH)
2. Somatotropin or growth hormone (GH)
3. Prolactin (PRL)
4. Thyrotropin or thyroid-stimulating hormone (TSH)
5. Luteinizing hormone (LH)
6. Follicle-stimulating hormone (FSH)

The hormones that play a central role in this thesis are detailed below.

Adrenocorticotropic hormone and the HPA-axis

The hypothalamus-pituitary-adrenal (HPA) axis is important in the physiology of the stress response. In addition, alterations in the HPA-axis are involved in depression (3;4), post-traumatic stress disorder (5), and other stress-related disorders.

In response to a stressful event, the hypothalamus secretes CRH into the hypothalamic-pituitary portal venous circulation. CRH, in turn, stimulates ACTH release from the pituitary. After ACTH is released into the bloodstream, it reaches the adrenal glands and stimulates the adrenal cortex to release cortisol and other steroids. In turn, cortisol has an inhibitory effect on CRH and ACTH secretion through a negative feedback mechanism (1;6). Cortisol is secreted in a pulsatile fashion and in a circadian rhythm. Plasma ACTH and cortisol concentrations are highest at the time of waking in the morning and decline during the day (1).

Growth hormone

The hypothalamus secretes GHRH to stimulate GH transcription and secretion from the pituitary in a pulsatile manner. The hypothalamus also secretes somatostatin, which inhibits GH secretion. GH secretion is related to emotional, physical, and chemical stress, including surgery, electroshock therapy, trauma, sepsis, and exercise (1). GH secretion is also affected by nutritional factors; subjects who are malnourished or fasting have increased GH secretion (7).

The primary function of GH is promotion of linear growth. GH is involved in bone remodeling, muscle growth, and immunomodulation. GH stimulates insulin-like growth factor-I (IGF-1) secretion in other tissues, especially the liver. Most of the growth promoting effects are caused by IGF-I. In turn, IGF-I inhibits GH secretion from the pituitary (1).

3. Pituitary adenomas

Cushing's disease

ACTH producing adenomas cause excessive cortisol production from the adrenal gland and the resultant hypercortisolism induces a constellation of signs and symptoms referred to as Cushing's disease. These ACTH secreting adenomas are almost always benign in origin. Cushing's disease is characterized by obesity with central fat distribution (see Figure 1b), moon face (see Figure 1a), plethora, osteopenia, proximal muscle weakness, striae (see Figure 1b), hirsutism, acne, poor wound healing, easy bruisability, superficial fungal infections, hypertension, glucose intolerance, and gonadal dysfunction (1).

Cushing's disease can be treated by selective removal of the pituitary adenoma via transsphenoidal surgery. When surgery is not curative, pituitary irradiation is

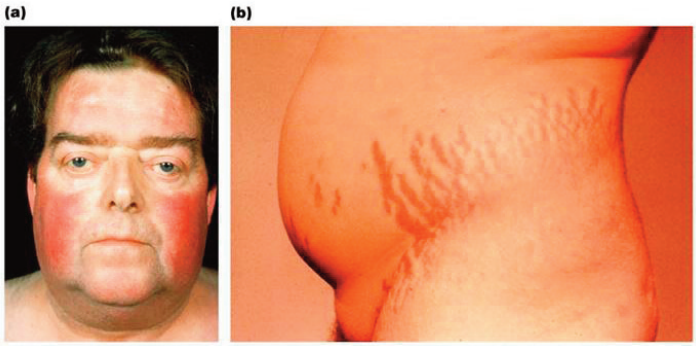

Figure 1. *Common clinical features in Cushing's disease, adapted from Pearson Education, Inc. 2007, publishing as Benjamin Cummings.*

one of the alternative treatment options (8). Bilateral adrenalectomy is the final definitive cure when surgery and irradiation fail. Bilateral adrenalectomy leads to lifelong daily glucocorticoid and mineralcorticoid replacement therapy (9). Currently, medical strategies are under investigation, for example with SOM 230 (10). Following cure of Cushing's disease, symptoms and mortality improve, but do not normalize (11). Patients frequently experience a corticosteroid withdrawal syndrome, with complaints like fatigue and muscle pain (12).

Acromegaly

GH-producing pituitary adenomas cause acromegaly (13). Acromegaly is a rare disease characterized by acral enlargement and coarse facial features (see Figure 2). The biochemical hallmarks are elevated growth hormone (GH) and insulin-like growth factor I (IGF-I) concentrations. GH overproduction in children leads to gigantism, while GH overproduction in adults leads to phenotypical changes like kyphosis, frontal bossing, macroglossia, soft tissue swelling with enlargement of hands and feet leading to increased ring and shoe size and organomegaly (14). Increased sweating, greasy skin, fatigue, paresthesias, headache, sleep disturbances, lethargy, and weight gain are often seen. Carpal tunnel syndrome, sleep apnea syndrome, hypertension, diabetes mellitus and arthropathy cardiomyopa-

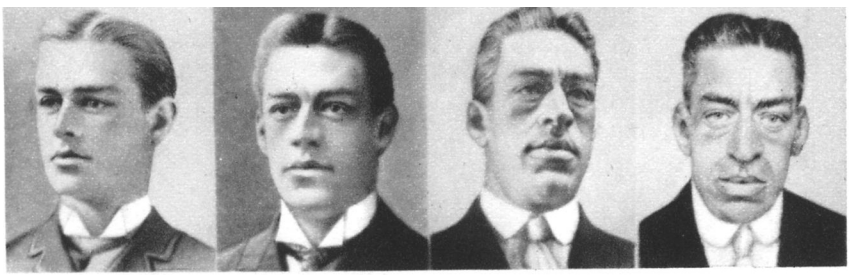

Figure 2. *Features of acromegaly over time, adapted from Chauvet, 1935.*

thy, valvular abnormalities, and malignancies especially of the gastro-intestinal tract are also well known problems in acromegaly (1;13;15-19). The early features of acromegaly are usually very subtle and difficult to diagnose. This is why diagnosis is often delayed, in most cases for more than ten years.
Acromegaly can be treated by selective removal of the pituitary adenoma via transsphenoidal surgery or by primary medical treatment with somatostatin analogs. Radiotherapy is not routinely used anymore because of side-effects, especially hypopituitarism. Following radiotherapy there is a long delay of many years in achieving normal GH levels (20). The GH receptor antagonist Pegvisomant is also a very effective medical treatment option, able to control GH excess in almost all patients (21).

Non-functioning pituitary macroadenoma

Non-functioning pituitary macroadenomas (NFMA) are benign in origin, although mass effects of the adenoma can cause clinical symptoms, such as visual field defects, pituitary insufficiency and chronic headache. Therefore, treatment is necessary in the majority of cases with clinical symptoms of mass effects (22;23). The primary therapy for patients with NFMA and visual field defects is transsphenoidal surgery (24-27). Additional radiotherapy can be used to reduce the regrowth of the adenoma. Although radiotherapy is successful in adenoma treatment, it can also induce complications, such as hypopituitarism (28;29) and in rare cases damage to the optic nerve (30). Since NFMAs are also classified as pituitary tumors and are treated in the same way as ACTH-secreting adenomas and GH-secreting adenomas, NFMAs can serve as a reference population to compare the effects of ACTH or GH overproduction *per se* versus the effects of pituitary adenomas and/or their treatment.

4. Illness perceptions

Persistent thoughts about a present disease and/or its treatment can influence general well-being. The sources of thoughts of a patient about the illness are diverse. They can be derived from information from doctors, relatives, friends, or media, but also from first hand experience with someone in the close proximity who suffers from an illness. Therefore, illness perceptions are subjective, may be partly or completely incorrect, and do not necessarily represent the medical status of the disease. Patients and their doctors may have (totally) discrepant perceptions of the severity of the disease and the success of treatment. This concept has hardly been elaborated for endocrine diseases and can be studied by measuring illness perceptions.

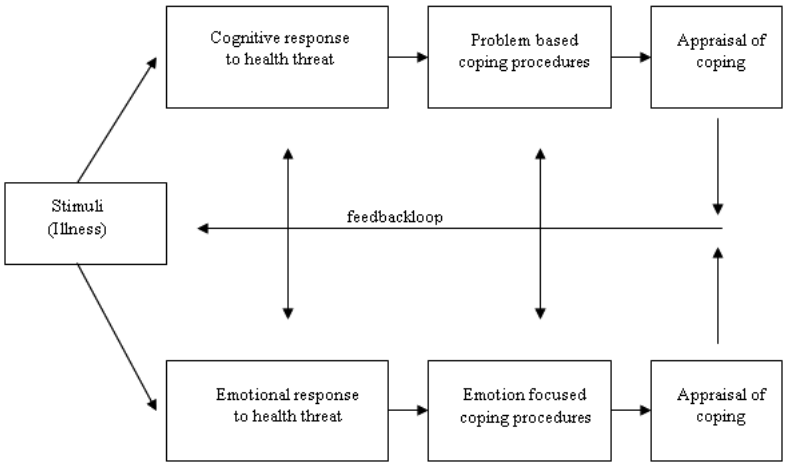

Figure 3. *The parallel process model (CSM), adapted from Leventhal et al., 2003 (31).*

Illness perceptions pertain to the way in which patients make sense of, and respond to, their illness. Illness perceptions are conceptualized in the parallel process model, later referred to as the Common Sense Model of self-regulation (CSM), which is depicted in Figure 3 (31). This CSM explains how patients generate both cognitive representations of, and emotional reactions to, their illness, integrating internal and external stimulus information with their pre-existing illness theory (32). Leventhal *et al.* (33) designed the CSM which starts from the premise that individuals are active problem solvers who make sense of a threat to their health by developing a cognitive representation of the threat, which determines how the individual responds. The specific procedures and strategies that are chosen by the patient for regulation of the health threat are defined by 1) the properties of the health threat, and 2) the resources that are available to the patient and the social context and culture (31).
Patients cluster representations or ideas about the illness around five cognitive components, which contain specific types of somatic and perceptual information about an illness threat:

1. The label that is used by the individual to describe the condition and the associated symptoms;
2. Beliefs about the cause of the condition;
3. Expectations about the likely duration of the condition;
4. The physical, psychological, and social consequences of the condition;
5. The extent to which the condition is amenable to cure and/or control.

These cognitive components are congruent with two basic propositions that underlie the CSM. The first proposition states that when people construct illness representations, they act as a common sense scientist. The second proposition states that the illness representations generate goals for self-management and that

these representations suggest procedures for goal attainment and criteria for evaluating response efficacy (31).

The components that form the illness representations determine the patients' coping procedures (34-36). Coping is the way in which someone reacts (behaviorally, cognitively, and emotionally) to situations that require adjustments in dealing with an adverse event and/or its consequences, for example an illness and its treatment (37). It is thought that both illness perceptions and coping strategies are important factors that influence medical, psychological, and behavioral outcomes and thereby determine quality of life (38-40).

5. Quality of life and psychological functioning

Quality of Life (QoL) refers to the perception of patients of their physical, mental, and social health. QoL has been studied in patients with pituitary adenomas with untreated and treated disease. QoL generally improves after treatment, but research indicates that QoL remains impaired even after successful treatment (41-44). There are disease specific impairments in QoL, which is also shown in Figure 4. A recent study by van der Klaauw *et al.* (45) reported that patients with long-term follow-up of acromegaly had the largest impairment in QoL, compared to patients after long-term follow-up of other pituitary adenomas. This difference is mostly due to the fact that patients with acromegaly reported impairment in physical performance and an increase in bodily pain. Patients with long-term remission of Cushing's disease also reported impairments in physical functioning. The authors concluded that QoL is most severely impaired in patients during long-term follow-up of successful biochemical disease control of acromegaly and Cush-

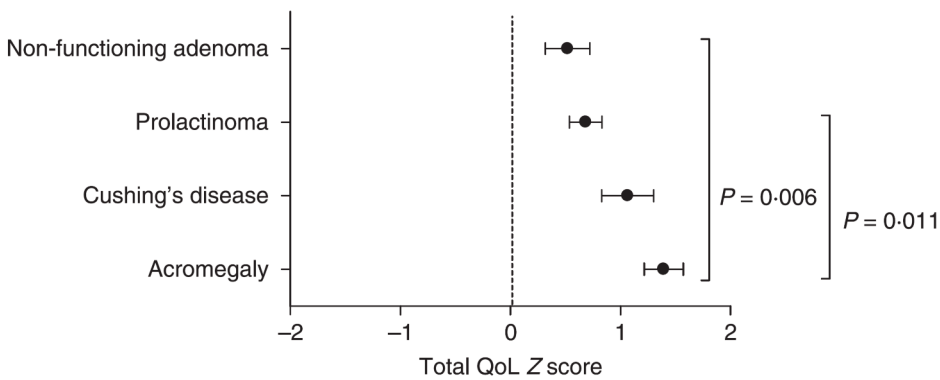

Figure 4. *Quality of life in pituitary adenomas (higher Z-score represents a worse QoL), adapted from Van der Klaauw et al., 2008 (45).*

ing's disease in comparison to patients with non-functioning pituitary adenoma or prolactinoma.

In those previous QoL studies, patients reported psychological impairments on various quality of life questionnaires, both general health and disease specific questionnaires. However, the QoL questionnaires are not designed to assess these psychological aspects thoroughly. There are, to date, several studies on psychological aspects (i.e. cognition and psychopathology) in patients with active Cushing's disease and acromegaly and some studies after short-term remission (<18 months) of these diseases (41;46-48;48-84). However, it is unclear to which extent impairments in cognitive function and the increase in prevalence of psychopathology are present in patients with (much longer duration) remission of Cushing's disease or acromegaly.

Psychological functioning in Cushing's disease

Patients with active Cushing's disease have cognitive impairments, especially in the memory domain. Previous studies reported impairments in memory, visual and spatial information, reasoning, verbal learning, and language performance (46-52). Structures important in cognitive functioning, like the hippocampus and cerebral cortex, are rich in glucocorticoid receptors and are therefore particularly vulnerable to the glucocorticoid excess present in Cushing's disease (49).
A large number of studies in humans and animal models have documented that prolonged, increased endogenous or exogenous exposure to glucocorticoids may have long-lasting adverse effects on behavioral and cognitive functions, due to functional and, over time, structural alterations in specific brain target areas (85-88). Following successful treatment of hypercortisolism, both physical and psychiatric signs and symptoms improve substantially (62;63).

Psychological functioning in acromegaly

Previous studies on acromegaly documented that patients with active acromegaly suffer from cognitive dysfunction, personality changes, and various forms of psychopathology (75-77;79;82-84). These observations suggest that the central nervous system is involved in the clinical syndrome of active acromegaly. This notion is supported by the presence of GH receptors in various brain areas outside the classical pathways of the GH-IGF-1 axis (89). Some of these structures are crucial for cognitive functioning, and influence mental status and personality through connections with the limbic system and frontal lobe (90). Many of the systemic changes induced by previous excess of GH and/or IGF-I are not completely reversed upon successful biochemical treatment of active acromegaly (91), which may also be true for the effects of GH and/or IGF-1 on the central nervous system. For instance, 36% of the patients with cured acromegaly showed elevated scores for anxiety and depression (41).

6. Scope of the present thesis

QoL is impaired in patients after treatment of pituitary adenomas, even during long-term follow-up. From previous studies in other (chronic) diseases it is evident that QoL and psychological factors, like illness perceptions and psychopathology, are related. Therefore, the aim of this thesis was to assess long-term psychological consequences of treated pituitary adenomas.

Illness perceptions and coping strategies

Although the decreased QoL may originate from persisting limitations due to irreversible effects of excessive hormone exposure, an alternative hypothesis is that the psychological impact of suffering from this disease results in quality of life reduction. This can be assessed by asking how patients perceive the effects of the pituitary adenoma and/or of its treatment. It was unknown how pituitary patients perceive their illness and its symptoms. We therefore explored illness perceptions in patients after long-term remission of Cushing's syndrome in **Chapter 2**, using a validated questionnaire, not previously used in endocrine diseases. We compared the illness perceptions of patients after long-term remission of Cushing's syndrome with various reference samples. We also studied the relation between QoL and illness perceptions.

In addition, we explored the illness perceptions of patients after long-term remission of acromegaly in **Chapter 3**. We also assessed the relationship between QoL and illness perceptions in these patients.

The components that form illness representations determine the coping procedures of patients. We therefore assessed these coping procedures in **Chapter 4** in patients with pituitary adenomas. We compared these patients to Dutch reference groups using a validated questionnaire on coping strategies.

The prevalence of cognitive impairment and psychopathology

Earlier studies on cognitive functioning in patients with treated Cushing's disease documented impaired cognitive function in some but not all studies. In addition, these studies included only small numbers of subjects, and patients were tested relatively short after treatment for Cushing's disease. It was unclear to which extent impairments in cognitive functioning remain present in patients with long duration of cure of Cushing's disease. Therefore, we evaluated cognitive functioning in patients after long-term remission of Cushing's disease in **Chapter 5**, and compared these data with those of age- and sex-matched controls. To assess to which extent treatment of pituitary adenomas *per se* affected our parameters, we additionally compared patients with long-term cure of Cushing's disease to patients treated for NFMA using Z-scores.

In addition, we also investigated the prevalence of psychopathology and maladaptive personality traits in patients during long-term remission of Cushing's disease. Patients with Cushing's disease were compared with age- and sex-matched controls as well as with patients treated for NFMA using Z-scores. The results of this analysis are described in **Chapter 6**. A review giving an overview of all studies on psychopathology and Cushing's disease is presented in **Chapter 7**. Cognitive functioning and prevalence of psychopathology in patients after long-term remission of acromegaly were analyzed in **Chapter 8**. The aim was to assess whether previous GH and/or IGF-I excess is associated with psychopathology, maladaptive personality traits, and cognitive dysfunction. We compared psychopathology, personality traits, and cognitive function between patients with long-term cure of acromegaly and age- and sex-matched controls as well as with patients treated for NFMA using Z-scores.

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