Understanding clinical outcome in patients with pituitary disease: a biopsychosocial approach

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Voor mijn oma's

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):

- 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).

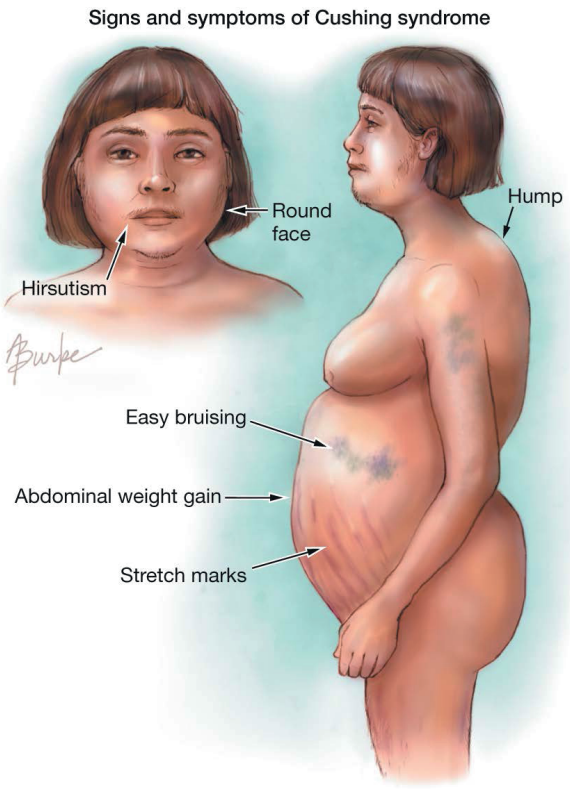

Figure 1. Signs in Cushing's disease, derived from Pluta et al. (11)

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).

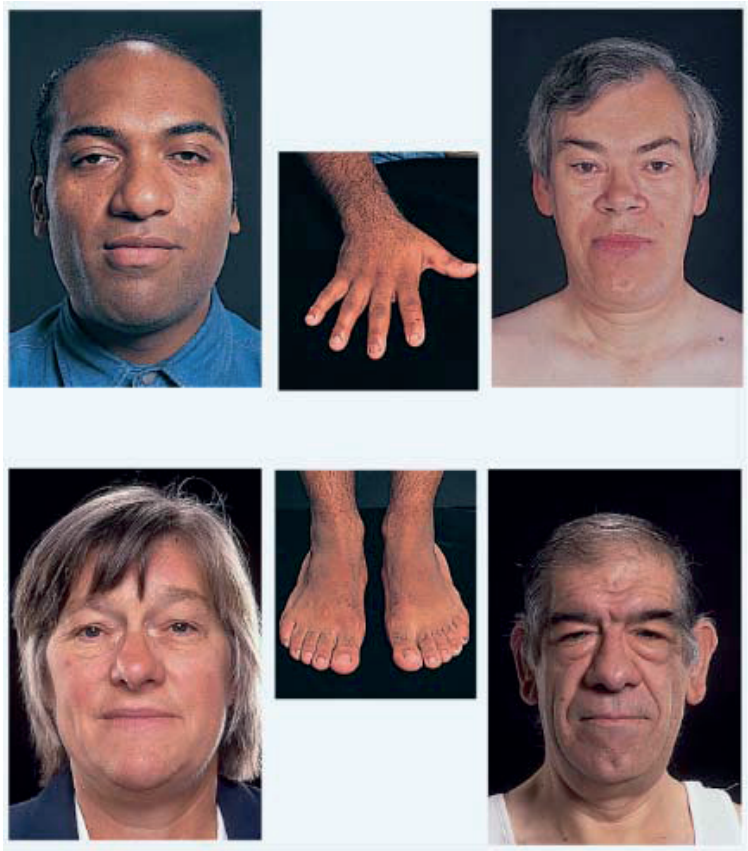

Figure 2. Signs in acromegaly, derived from Levy & Howlett (6).

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 oligomenorrhoea 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

Insufficiency of	Replacement therapy
Cortisol	Hydrocortisone: 15-40 mg per day divided into two to three doses
Thyroid hormones	Levothyroxine: 1.6 µg/kg per day (100-200 µg usually adequate)
Gonadotropic hormones	Adrogel: 50-100 mg per day (males) Combination estrogen/progestin (females)
Growth hormone	Growth hormone: 2-5 µg/kg per day

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 examine 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 models states that health can be thought of as a continuum of increasing biological, psychological and social complexity, with on the one end 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

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.

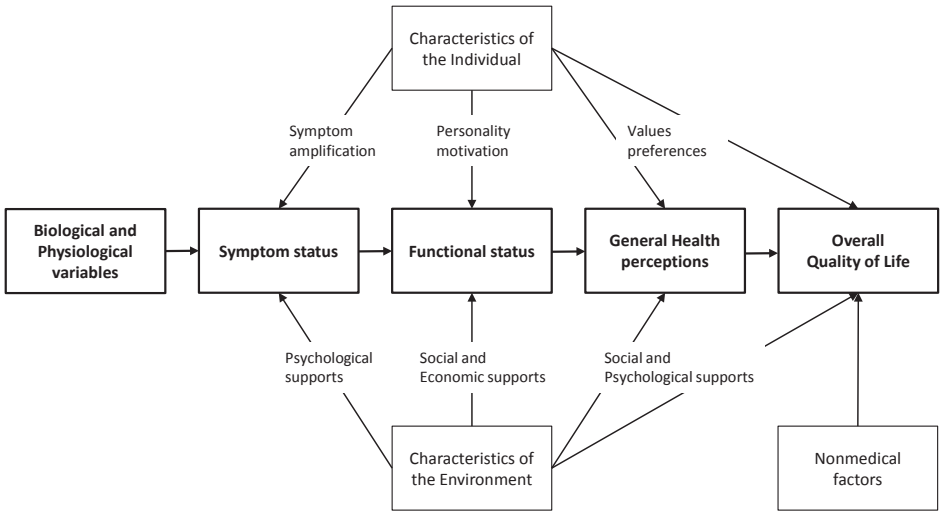

Figure 3. Wilson-Cleary model of QoL (35).
Biological and Physiological variables: function of cell, organs, and organ systems e.g., diagnoses, laboratory values, measures of physiological function, and physical examination findings.
Symptom status: a patient's perception of an abnormal physical, emotional 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).

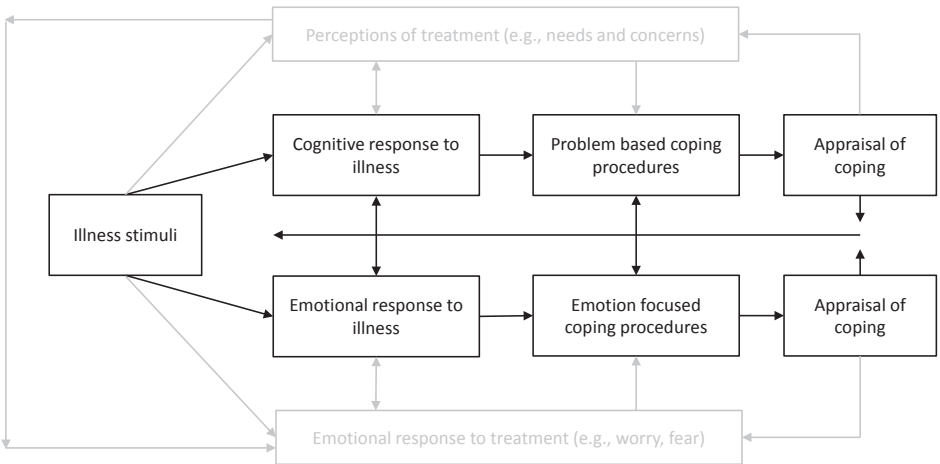

Figure 4. The Common-Sense Model of Self-Regulation (black) extended with beliefs about medicine (grey). Adapted from Horne (59).

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).

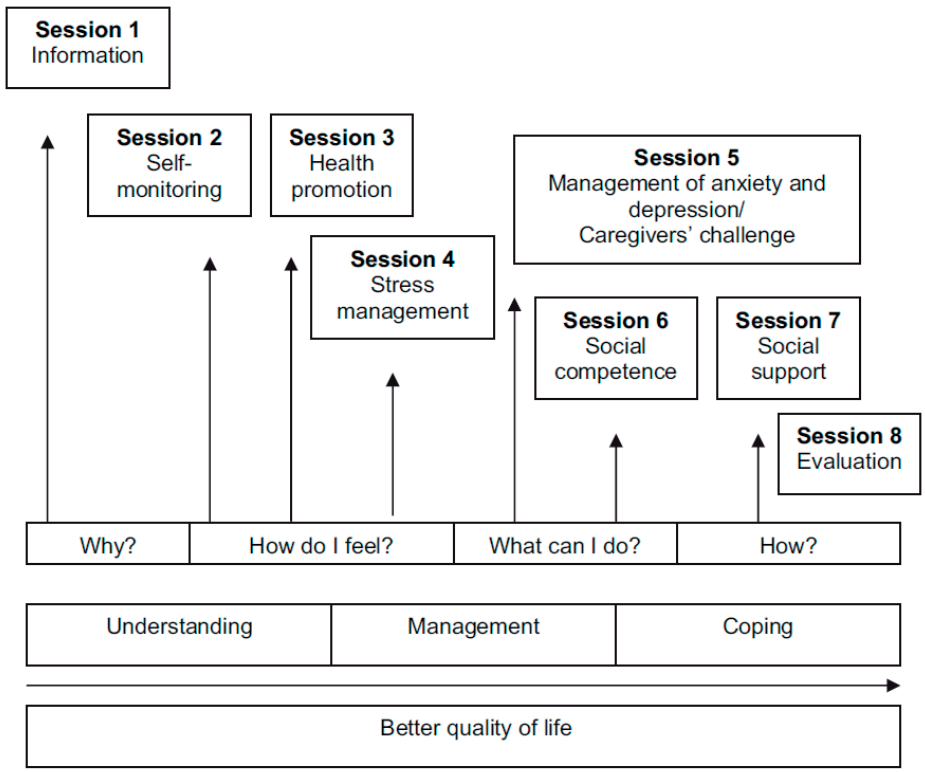

Figure 5. Themes and aims of the patient education programme. Figure derived from A'Campo et al. (66)

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.

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CHAPTER 2

Cushing's syndrome causes irreversible effects on the human brain: a systematic review of structural and functional MRI studies

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ABSTRACT

Background: Cushing's syndrome is characterized by excessive exposure to cortisol, and is associated with both metabolic and behavioral abnormalities. Symptoms improve substantially after biochemical cure, but may persist during long-term remission. The causes for persistent morbidity are probably multi-factorial, including a profound effect of cortisol excess on the brain, a major target area for glucocorticoids.

Objective: To review publications evaluating brain characteristics in patients with Cushing's syndrome using magnetic resonance imaging (MRI).

Methods: Systematic review of literature published in Pubmed, Embase, Web of Knowledge, and Cochrane databases.

Results: Nineteen studies using MRI in patients with Cushing's syndrome were selected, including studies in patients with active disease, patients in long-term remission and longitudinal studies, covering a total of 339 unique patients. Patients with active disease showed smaller hippocampal volumes, enlarged ventricles, and cerebral atrophy as well as alterations in neurochemical concentrations and functional activity. After abrogation of cortisol excess, the reversibility of structural and neurochemical alterations was incomplete after long-term remission. MRI findings were related to clinical characteristics (i.e. cortisol levels, duration of exposure to hypercortisolism, current age, age at diagnosis, triglyceride levels) and behavioral outcome (i.e. cognitive and emotional functioning, mood, and quality of life).

Conclusion: Patients with active Cushing's syndrome demonstrate brain abnormalities, which only partly recover after biochemical cure, since these still occur even after long-term remission. Cushing's syndrome might be considered as a human model of nature that provides a keyhole perspective of the neurotoxic effects of exogenous glucocorticoids on the brain.

INTRODUCTION

Cushing's syndrome (CS) is a rare clinical syndrome characterized by excessive endogenous exposure to cortisol due to various etiologies. The majority of patients have ACTH-producing pituitary tumors (i.e. Cushing's disease (CD)); other causes include adrenal tumors or ectopic ACTH secreting tumors. CS manifests all characteristic features of excessive stress hormone exposure, i.e. psychopathology, gonadal dysfunction, hirsutism, abnormal (central) fat distribution, thin skin with easy bruisability, hypertension, muscle weakness, and osteoporosis (1). Patients are treated with surgery, and in case surgical remission is not obtained, radiotherapy and/or with medical treatment (2). Although symptoms improve substantially after biochemical cure, cardiovascular morbidity and mortality remained elevated (3-5). Furthermore, despite long-term remission, patients with CS reported impaired quality of life (6), higher prevalence of psychopathology, and demonstrated impairments in cognitive functioning (7;8). It is likely that the causes for persistent morbidity are multi-factorial, including intrinsic imperfections of surgical or endocrine replacement therapy, and the impact of living with a chronic disease, but also irreversible effects of cortisol excess on the central nervous system during remission that may affect personality, behavior, and metabolism cannot be neglected. Whereas the attention for the presence of psychopathology and impairments in cognitive functioning in patients with active, as well as remitted CS is self-evident, the number of studies evaluating brain structures and activity in patients with CS has been rather limited.

The detrimental effects of hypercortisolism, such as in CS, on the human brain were first highlighted in autopsy reports, describing a lighter brain and enlarged ventricles in deceased CS patients (9). The first *in vivo* studies in the human evaluating these brain characteristics were performed in patients with CS using pneumoencephalography. In 1971, Momose and colleagues used pneumoencephalography in 31 patients with CD, and demonstrated cerebral cortical atrophy in 90% of the patients and cerebellar cortical atrophy in 74% of the patients compared to normal references derived from the literature (10). The introduction of the magnetic resonance imaging (MRI) scanner in 1977 enabled the assessment of brain volumes and brain structures more accurately and in more detail. In 1992, Starkman and colleagues were the first to report on hippocampal volumes obtained from routine pituitary MRI diagnostics of patients with active CS, and compared these with healthy control data derived from the literature. Hippocampal volume was decreased during active CS (11), but a partial recovery could be observed after successful treatment (12;13). However, new imaging techniques are emerging that enable to better evaluate brain structures and functioning.

The aim of the present study was to systematically review the literature on structural and functional changes in the brain identified with (MRI) in patients with CS. The secondary aim was to review potential associations between brain characteristics and disease status, cognitive functioning, psychopathology, and general well-being.

METHODS

Search strategy and data extraction

The following electronic databases were searched: Pubmed, Embase, Web of Knowledge, and Cochrane. The search was performed on August 5 2014. We composed a search strategy focusing on MRI studies in patients with Cushing's disease and Cushing's syndrome (see Supplement 1 for the complete search strategy). Studies on patients with CS due to the use of exogenous corticosteroids were excluded. Data extraction and eligibility were assessed by two independent investigators (C.D.A. and A.M.P.). Inconsistencies were resolved by consensus. All references were checked for additional papers. The following data were extracted: 1) sample size, 2) gender distribution, 3) mean age of included patients, 4) disease status (active/remission), 5) estimated duration of exposure to hypercortisolism, 6) methods used, and 7) results.

Quality assessment

Due to different designs and methods in the studies that were identified, it was not possible to use a pre-existing quality assessment tool. Therefore, we formulated a quality assessment list adapted from the list used in a systematic review on neuroimaging studies in patients with multiple sclerosis (14). Sixteen items were defined: *clear study objective*, *inclusion/exclusion criteria*, *population demographics*, *diagnostic criteria and/or remission criteria*, *estimation of disease duration*, *composition of patient group* (i.e. heterogeneous or homogenous regarding to origin of CS (pituitary-adrenal) and disease status (active-remission)), *sample size*, *design* (retrospective assessment based on scans obtained from routine pituitary evaluation, or prospective or cross-sectional), *inclusion of a control group* assessed in the same manner as the patient group, *assessment of cognitive and psychological functioning*, *imaging protocol*, *scanner type* (1T, 1.5T or 3T), *strength of effect* reported, *multivariate analysis*, and *discussion of limitations*. Total individual quality scores ranged from 0 to 20 points (see Table 1). The quality of each study was assessed by two independent reviewers (C.D.A. and A.M.P) and discrepancies were discussed and resolved by consensus. Total scores were calculated as percentages ("individual total score" / 20 x 100%). The median of the quality scores was 75% and was used as cut-off point, with papers with quality scores ≥75% being considered as high quality papers. Given the low number of studies, studies were not excluded based on the quality assessment.

Table 1. List of criteria used for the quality assessment

1	Research objective	Yes=1 / No=0
2	Inclusion/exclusion criteria	Yes=1 / No=0
3	Population demographics (at least gender, age, education*)	Yes=1 / No=0
4	Diagnostic criteria and/or remission criteria	Yes=1 / No=0
5	Estimation of disease duration	Yes=1 / No=0
6	Composition of patient groups	Heterogeneous (CS/CD)=0 Homogenous CS-CD=1
7		Heterogeneous (active/remission)=0 Homogenous (active-remission)=1
8	Sample size	n<20 =0 n>20 =1
9	Design	Retrospective=0 Prospective =1 Cross-sectional=1
10	Control group included	No control group=0 Control group=1 Matched control group=2
11	Cognitive measures (including cognitive tasks during fMRI)	Yes=1 / No=0
12	Psychological measures	Yes=1 / No=0
13	Imaging protocol	Yes=1 / No=0
14	Scanner	1T=1 / 1.5T=2 / 3T=3
15	Strength of effect	Yes=1 / No=0
16	Multivariate analysis	Yes=1 / No=0
17	Limitations discussed	Yes=1 / No=0
		Total score

*Or IQ in case of studies in children.

RESULTS

Literature overview

The literature search identified 142 publications, of which 16 were eligible for inclusion. By scanning references of included articles, three articles were added to the selection. Therefore, the final selection consisted of 19 articles including a total number of 339 unique patients (Table 3, Figure 1). This selection consisted of six longitudinal studies, 11 cross-sectional studies, and two studies using both designs. The majority of the studies used structural MRI (n=14), three studies used proton magnetic resonance spectroscopy (H-MRS), and two studies used functional MRI. Nine studies combined MRI outcome with the assessment of cognitive functioning. Further information on the MRI techniques, neuropsychological tests, and behavioral measures are provided in the Supplementary file 2.

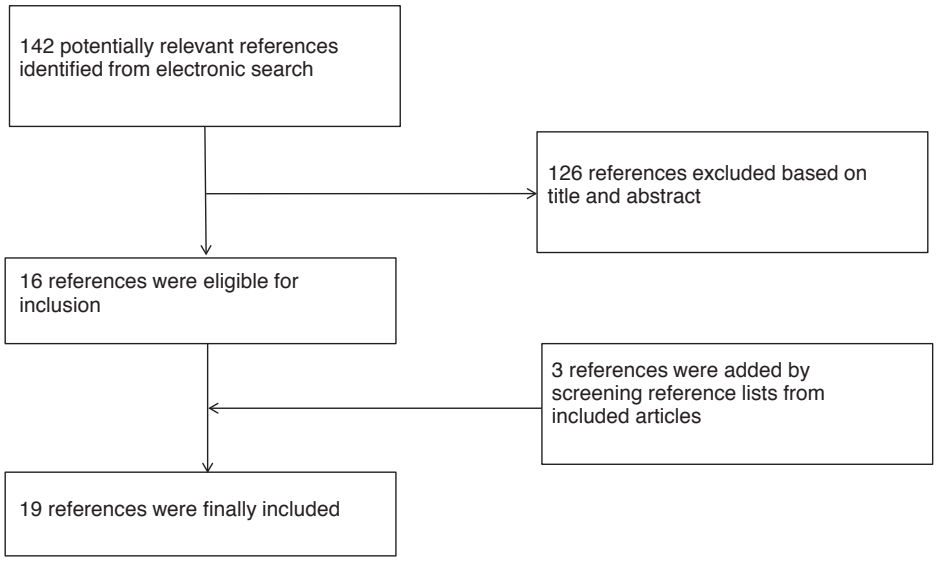

Figure 1. Flow-diagram of selection and exclusion stages.

Table 2. Quality assessment

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Individual score	Quality score
Starkman, 1992	1	1	1	1	1	0	1	0	0	0	1	0	1	2	1	0	1	12	60%
Starkman, 1999	1	1	0	1	1	1	1	1	1	0	0	0	1	2	1	1	1	14	70%
Khiat, 1999	1	1	0	1	0	0	1	0	1	1	0	0	1	2	1	0	1	11	55%
Khiat, 2000	1	1	0	1	0	0	1	0	1	1	0	0	1	2	1	0	0	10	50%
Simmons, 2000	1	0	0	0	0	1	1	1	0	1	0	0	0	0	1	0	0	6	30%
Bourdeau, 2002	1	1	0	1	0	1	1	1	1	1	0	0	1	2	1	0	1	13	65%
Starkman, 2003	1	1	0	1	1	1	1	1	1	0	1	1	1	2	1	1	0	15	**75%**
Merke, 2005	1	1	1	1	1	0	1	0	1	2	1	1	1	2	1	0	1	16	**80%**
Hook, 2007	1	1	1	1	1	1	1	1	1	0	1	1	1	2	1	1	1	17	**85%**
Starkman, 2007	1	1	0	1	1	1	1	1	1	0	0	1	1	2	1	1	1	15	**75%**
Maheu, 2008	1	1	1	1	1	0	1	0	1	1	1	0	1	3	1	1	1	16	**80%**
Resmini, 2011	1	1	1	1	1	0	0	1	1	2	1	0	1	3	1	1	1	17	**85%**
Toffanin, 2011	1	1	1	1	1	1	1	0	1	0	0	0	1	1	1	1	1	13	65%
Langenecker, 2012	1	1	1	1	1	0	1	1	1	1	0	1	1	3	1	1	1	17	**85%**
Andela, 2013	1	1	1	1	1	1	1	1	1	2	1	1	1	3	1	1	1	20	**100%**
Resmini, 2013	1	1	1	1	1	0	1	0	1	2	0	0	1	3	1	0	1	15	**75%**
Crespo, 2014	1	1	1	1	1	0	0	1	1	2	1	0	1	3	1	1	1	17	**85%**
Santos, 2014	1	1	1	1	1	0	1	1	1	2	1	1	1	3	1	0	1	18	**90%**
Van der Werff, 2014	1	1	1	1	1	1	1	1	1	2	1	1	1	3	1	1	1	20	**100%**

The 17 quality items were scored following the criteria listed in table 1. **Bold**: quality score≥75%.

Quality assessment

The individual quality scores of the studies ranged from 30 to 100%, with a median of 75%. Overall, the more recent articles had higher quality scores, which can partly be explained by the transition from using 1.5T scanners to 3T scanners, and the absence of applying multivariate analysis in the earlier studies. Furthermore, 53% of the studies (n=10) included patients with CS of both pituitary and adrenal origin, and approximately half of the studies did not include psychological (n=11) and/or cognitive measures (n=9).

Endocrine evaluation

Diagnostic criteria for CS were clearly defined in thirteen studies (68%). Five studies (26%) did not describe diagnostic criteria, but mentioned criteria of remission (15-19). One study did neither describe diagnostic nor remission criteria (20).

Described diagnostic criteria were clinical features (truncal obesity, skin and muscle arthophy, moon facies) (11-13;21), elevated urinary free cortisol (UFC) (11-13;21-29), elevated cortisol secretion rates (11-13;21;23-25;30), elevated midnight salivary cortisol (29;31), absence of blunted circadian rhythm of cortisol secretion (11-13;21;26;27;30;32;33), elevated ACTH levels (in CD only) (12;13;21;23;24), lack of suppression after low dose dexamethasone ((1 mg) (22;25;29;33), (2mg) (12;13;21), dose not mentioned (23;24)) or 50% suppression after high dose (8mg) (12;13;21), and abnormal response to CRH (30).

Described remission criteria were normal UFC (15-19), adrenal insufficiency, morning cortisol suppression after low dose dexamethasone overnight (1mg) (17-19), or less than 30 mg hydrocortisone per day (15).

All studies (except four (15;20;23;24)) reported on the estimated duration of hypercortisolism, which was based on patient's history and old photographs. In studies that included pediatric patients with CS, the onset of decreased growth velocity was used (26;27). The mean estimated duration of hypercortisolism ranged from 2.6 to 7.9 years.

MRI outcome in patients with active Cushing's syndrome

The first studies evaluating brain volume with MRI in patients with active CS used MRI scans obtained from routine pituitary evaluation. In 1992, Starkman et al. reported hippocampal volume to be outside the 95% confidence interval of healthy control data derived from the literature in 27% of the patients (total sample size n=12) (11). In a larger cohort (n=63), patients with CS were reported to have more brain atrophy compared to controls (Figure 2) (20). In agreement, Bourdeau and colleagues demonstrated that patients with active CS had increased third ventricle diameter, bicaudate diameter, and cerebral atrophy, compared to control patients with no sellar tumors (15). A recent study found smaller grey matter volumes of the bilateral cerebellum in patients with active CS compared to controls (19). When investigating the effect of CS on the developing brain, children with CS were found to have smaller cerebral volumes, larger ventricles and smaller amygdala than controls (27).

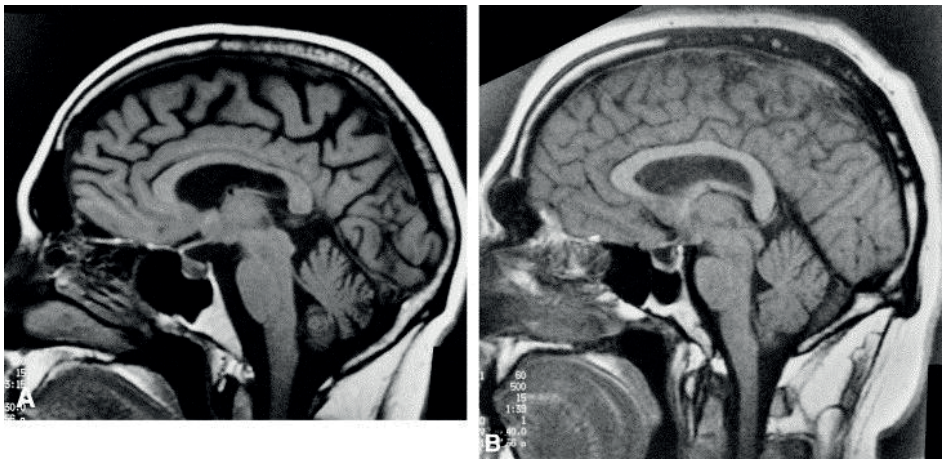

Figure 2. Brain atrophy in a patient with active CD vs. healthy control.
T1-weighted sagittal MRIs of a 32-year-old patient with Cushing's disease (A) and age- and sex-matched control (B) (20).

Khiat et al. (1999) used proton magnetic resonance spectroscopy (H-MRS), a non-invasive tool that can be used to evaluate changes in cerebral metabolites. Patients with active CS had decreased ratios of creatine and phosphocreatine ratios (markers of energy metabolism) and decreased choline-containing compounds (a membrane marker) in frontal and thalamic areas, indicating persistent alterations in the cholinergic system (23).

Only two studies have investigated patients with active CS with functional magnetic resonance imaging (fMRI). Using an emotional faces task, adult patients 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. These findings indicated alterations in brain activity in regions used for emotion processing (25). Furthermore, adolescents with active CS demonstrated increased activation in the left amygdala and right anterior hippocampus in response to successful encoding during the performance of a facial memory task. These results point toward alterations in brain activity in substrates related to depressive symptoms and emotional memory. Interestingly, none of the adolescents suffered from psychiatric disease, therefore the authors postulated that the exaggerated amygdala activity and exposure to elevated cortisol levels is not sufficient for initiating depression in adolescents (26).

Longitudinal studies assessing the potential reversibility of brain abnormalities

Eight studies evaluated the potential reversibility of alterations in the brain after correction of hypercortisolism (mean duration of follow-up between 6 to 40 months).

Correction of hypercortisolism increased hippocampal volume (12), and decreased third ventricle- and bicaudate diameter, and regressed brain atrophy (15). Toffanin et al. reported

a significant increase in right and left hippocampus head volumes in CD patients after transsphenoidal surgery, with no significant increase in the body and tail of the hippocampus, suggesting that the head of the hippocampus is more sensitive to excessive cortisol exposure (33). Recovery in metabolite concentrations was also accompanied by an increase in thalamic and frontal choline levels up to six months after correction of hypercortisolism, indicating improvement in cholinergic system function (23). Children with CS demonstrated an increase in cerebral volumes and a decrease in ventricular volumes after surgery and total cerebral volume and ventricular size after one year of follow-up were comparable to age-matched controls (27).

MRI outcome in patients in long-term remission of Cushing's syndrome

Six studies evaluated patients in remission of CS using a cross-sectional design and identified structural, functional and biochemical abnormalities. The average duration of remission ranged from 3.4-11.9 years.

Resmini et al. found no differences between patients with active disease and patients in remission, and therefore analyzed these patients as one group. They found no differences in hippocampal volume between patients and healthy matched controls, but total grey matter (cortical and subcortical) and cortical grey matter were smaller in patients compared to controls (17). In 2013, Andela et al. found a smaller grey matter volumes of the anterior cingulate cortex and larger grey matter volumes of the left posterior lobe of the cerebellum in CD patients in long-term remission compared to healthy matched controls (figure 3) (22), whereas Santos and colleagues found no differences in cerebellar volumes between patients in remission and controls (19). Recently, Crespo et al. evaluated cortical thickness in medically treated eucortisolemic patients and patients in remission and demonstrated that patients with CS had decreased cortical thickness when compared to controls (16).

At present, only one study has evaluated white matter integrity in patients with long-term remission of CD and demonstrated widespread reductions of integrity in white matter tracts throughout the brain (29).

Finally, using H-MRS, Resmini et al. demonstrated lower N-Acetyl-Aspartate ratios (marker of neuronal density, integrity, and variability) in the bilateral hippocampus in patients in remission of CS compared to controls, reflecting neuronal damage. Furthermore, patients demonstrated higher Glutamate (excitatory neurotransmitter) and Glutamine (glial marker) levels in both hippocampi, indicating proliferation as a repair mechanism. The authors postulated that these persisted alteration in biochemical markers in the brain could be related to glucocorticoid neurotoxicity (18).

Associations between brain abnormalities and clinical characteristics

Several studies found associations between structural and functional brain abnormalities and clinical and laboratory characteristics in patients with CS.

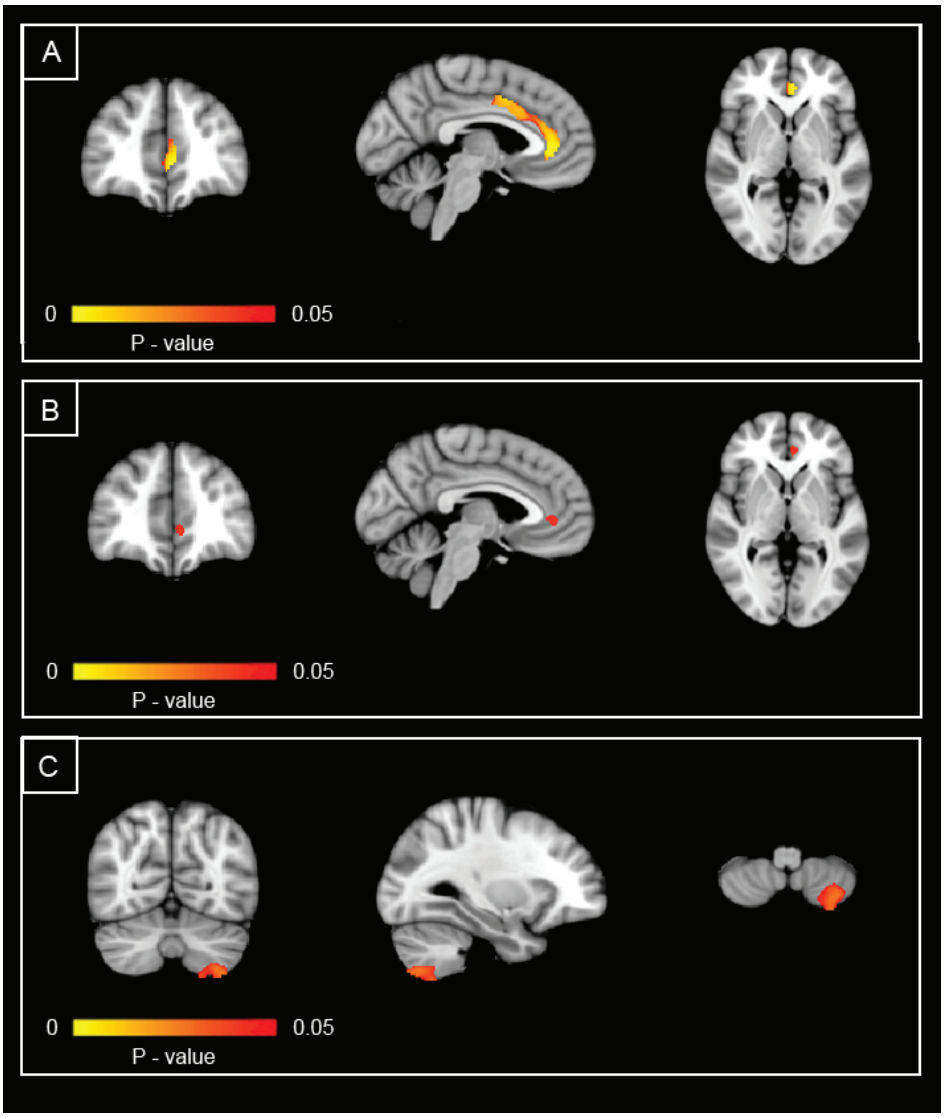

Figure 3. Grey matter volumes in patients after long-term remission of CD.
(A) Results of regions of interest analysis, with lesser grey matter volumes in patients than in controls (P<0.05; 617 voxels, 2mm isotropic). (B) Results of whole brain analysis with lesser grey matter volumes in patients than in controls (P<0.05; 37 voxels, 2mm isotropic). (C) Results of whole brain analysis with greater grey matter volumes in patients than in controls (P<0.05; 323 voxels, 2mm isotropic). The left hemisphere corresponds with the right side of the image (22).

In patients with active disease, hippocampal volumes were negatively correlated with plasma cortisol levels, but not with UFC, current age and cortisol levels multiplied by the estimated duration of disease (11). In functional MRI studies in active disease dorsal anterior cingulate activation during emotional task was positively associated with percent decline

in ACTH from morning peak to afternoon nadir, but not with percent cortisol decline from morning peak to afternoon nadir (25). On the other hand, in adolescents with active disease left amygdala activation and right anterior hippocampal activation during a facial memory task was not correlated with 24-hr UFC levels (26). Bicaudate diameter was correlated with UFC in patients with active CD, whereas no associations were found with degree of cerebral atrophy. In patients with adrenal CS, UFC did correlate with the degree of cerebral atrophy (15). Duration of hypercortisolism was negatively associated with subcortical grey matter volume (17), and significant differences in brain atrophy were found between subsets of patients with a long disease duration compared to patients with shorter disease duration (20). Furthermore, grey matter volume of the bilateral cerebellum, was negatively associated with age at diagnosis and triglyceride levels, but not with current age, level of cholesterol, glucose, UFC, duration of exposure to hypercortisolism (19). Furthermore, cortical thickness was not associated with duration of eucortisolism, duration of prior hypercortisolism and UFC (16).

Increase in hippocampal volume after correction of hypercortisolism was negatively associated with current age (12), and significant differences in degree of brain atrophy were found between subsets of patients of different age (20). In contrast, Bourdeau et al. found no correlation between brain volume and current age, although this could be related to the relatively young sample of patients included (15). An increase in hippocampal volume was associated with a decrease in UFC after treatment (12;13;21), but not with reduction in plasma cortisol, duration of disease or the number of months relapsed since treatment (21;30). Increase in right caudate head volume (CHV) was also associated with decrease in UFC, while increase in left CHV and right and left CHV together were not associated with change in UFC (13;21).

In patients with long-term remission no correlations were found between grey matter volumes of the ACC and cerebellum and white matter integrity, and estimated duration of hypercortisolism, duration of remission and clinical severity (22;29), nor between NAA and GLX ratios and duration of hypercortisolism and duration of remission (18).

Associations between brain abnormalities and behavioral outcome/measures

In several studies associations between structural and functional brain abnormalities and behavioral measures, especially in memory and mood domains, were found.

In patients with active disease, hippocampal volumes were positively associated with verbal learning and verbal recall (11). Increased activation of the left lateral posterior/pulvinar nuclei of the thalamus and the left middle frontal gyrus were positively correlated with accuracy in emotion identification in patients with active disease, whereas activation in the left superior parietal lobule was not significantly correlated with accuracy of emotion identification (25). In adolescents with active CS, left amygdala activation and right anterior hippocampal activation did not correlate with the performance of a facial memory task (26). Increase in hippocampal volume after correction of hypercortisolism was positively associ-

Table 3. Study characteristics of MRI studies in patients with CS

Author, year	N	Gender (m/f)	Age mean ± SD	Active/treated	Estimated duration of hypercortisolism	Procedure & Method	Evaluated brain areas	Outcomes
CROSS-SECTIONAL								
Starkman, 1992	12	2/10	37.3±13.95	9 active CD 3 active CS *1 healthy control*	Range 1-4 yr	1.5T MRI Scans obtained from routine pituitary MRI Volumes were manually traced and digitally calculated Neuropsychological tests: WMS, WAIS	Dentate gyrus. Hippocampus proper, subiculum	HFV of 27% of the patients fell outside the 95% CI for normal subjects. An association was found between reduced HFV and verbal learning and memory tasks. HFV was negatively correlated with plasma cortisol levels.
Khiat, 1999	13	0/13	Mean: 42.0 (range 21-64)	6 active CD 7 active CS *40 healthy controls*	NA	1.5T MRI H-MRS Metabolites were quantified	2 cm3 localized in the thalamic, frontal and temporal area of the left hemisphere	Patients demonstrated a decrease in Cho/Cr ration in frontal and thalamic areas. Patients with CS demonstrated a larger reduction, compared to patients with CD.
Simmons, 2000	63	48/15	NA	63 active CD *63 controls with non-ACTH producing sellar pathology, age and gender matched*	NA	CT/MRI obtained during treatment period Atrophy was rated	Whole brain	CD patients demonstrated more atrophy than controls. After stratifying for age and years of disease, no differences were found between patients and control when they were older than 60 yr, or when disease duration was shorter than 1 yr or between 4-5 yr.
Bourdeau, 2002¥	36 /2**	9/29	41.3±12.0	21 active CD 17 active CS *18 controls with non-ACTH producing sellar tumors* *20 controls with no sellar tumors*	NA	CT and/or MRI obtained from routine pituitary evaluation Measurement of diameters and subjective estimation of degree of cerebral atrophy	Third ventricle Bicaudate Whole brain	Third ventricle diameter, bicaudate diameter, and the subjective evaluation of brain atrophy were increased in patients compared to controls.

Table 3. Study characteristics of MRI studies in patients with CS (continued)

Author, year	N	Gender (m/f)	Age mean ± SD	Active/treated	Estimated duration of hypercortisolism	Procedure & Method	Evaluated brain areas	Outcomes
Merke, 2005¥	11	5/6	12.1±3.4	10 active CD 1 active CS *10 healthy age and gender matched controls*	4.4 ± 1.2	1.5T MRI Volumes were manually traced and quantified Total cerebral volume was quantified automatically Neuropsychological tests: PANESS, WISC, WAIS, CVLT-C, Woodstock-Johnson Psychoeducational Battery-R: Test Achievement Psychological assessment: BASC	Cerebrum, ventricles, temporal lobe, hippocampus amygdala	CS had smaller total cerebral volumes, lager ventricles and smaller amygdala volumes, HV was smaller, but not significant compared to controls
Maheu, 2008	12	4/8	13.5±2.9	10 active CD 2 active CS *22 healthy controls*	Mean 2.6 yr (range 1-4.5)	3T fMRI Face Memory Task BOLD signal	Amygdala Anterior hippocampus	Patients demonstrated increased activation in the left amygdala and right anterior hippocampus in response to successful encoding compared to controls.
Langenecker, 2012	21	4/17	34.4±14.9	20 active CD 1 active CS *21 healthy controls*	32.4±23.7 months	3T fMRI Facial Emotion Perception Test BOLD signal	Hippocampus Amygdala Whole brain	Patients had less activation in the left anterior superior temporal gyrus, and higher activation in the frontal, medial, and subcortical regions. Elevated activation of the left middle frontal and lateral posterior pulvinar areas was positively correlated with accuracy in emotion identification.
Resmini, 2012	33	6/27	44.8±11.8	7 active CD 4 active CS 18 remission CD 4 remission CS Average duration of remission:7.3±2.4yr *34 healthy age-, gender, education matched controls*	5.5±3.7 yr	3T MRI Volumes were automatically segmented and measured Neuropsychological tests: RAVLT, ROCF	Hippocampus Cortical GM Subcortical GM	No differences in HV between CS and controls. Patients with severe memory impairment showed smaller HV than controls. Total GM and cortical GM were decreased in CS patients. Subcortical GM was only reduced in patients with severe memory impairment.

Table 3. Study characteristics of MRI studies in patients with CS (continued)

Author, year	N	Gender (m/f)	Age mean ± SD	Active/treated	Estimated duration of hypercortisolism	Procedure & Method	Evaluated brain areas	Outcomes
Andela & Van der Werff, 2013	25	4/21	45±8	25 CD remission, Average duration of remission:11.2±8.2yr *25 healthy age-, gender, education matched controls*	7.9±7.9 yr	3T MRI Harvard-oxford cortical and subcortical structural atlases were used to create a mask Psychological and cognitive measures: MADRS, IDS, BAI, FQ, AS, IS, CFQ Physical questionnaire: CSI	Hippocampus, amygdala, ACC Whole brain	Patients demonstrated smaller GM volumes of the ACC and greater GM volumes of the left posterior lobe, compared to controls. Differences in GM were not associated psychological-, cognitive-, or clinical measures.
Resmini, 2013	18 ^	3/15	44.8±12.5	15 remission CD 3 remission CS Average duration of remission:8.5±3.2yr *18 age-, education matched healthy controls*	4.7±2.6 yr	3T MRI H-MRS Measurement of metabolic peaks	Hippocampus head	Patients showed decreased NAA levels in the hippocampi, and increased levels of Glx.
Van der Werff & Andela, 2014	22†	4/18	42.42±7.33	22 remission CD Average duration of remission:11.9±8.5yr *22 healthy age-, gender, education matched controls*	6.73±5.39 yr	3T MRI Johns Hopkins University WM atlas was used to create a mask Psychological and cognitive measures: MADRS, IDS, BAI, FQ, AS, IS, CFQ Physical questionnaire: CSI	Bilateral cingulate cingulum Bilateral hippocampal cingulum Bilateral uncinated fasciculus Corpus callosum Whole brain	Patients demonstrated widespread changes of WM integrity of the whole brain. Reduced WM integrity in the uncinated fasciculus was associated with severity of depressive symptoms.
Santos, 2014	36	6/30	Active 44.2±9.3 Remission 41.9±10.4	10 active CD 5 active CS 18 remission CD 3 remission CS Average duration of remission: NA *36 healthy controls matched for age, gender, and education*	Active 62.2±59.1 months Remission 61.8±32.2 months	3T MRI Volumes were automatically segmented and measured Neuropsychological tests: Animals, WAIS, BNT, FAS, Grooved Pegboard, ROCF, SDMT, TMT, WCST QoL: CushingQoL	Cerebellum	Patients had smaller GM volumes of the bilateral cerebellum, compared to controls. GM of the cerebellum negatively correlated with triglyceride levels and age at diagnosis. Left GM volumes correlated positively with visual memory performance, and right GM volume was positively correlated with QoL.

Table 3. Study characteristics of MRI studies in patients with CS (continued)

Author, year	N	Gender (m/f)	Age mean ± SD	Active/treated	Estimated duration of hypercortisolism	Procedure & Method	Evaluated brain areas	Outcomes
Crespo, 2014	35	5/30	Medically treated: 41.4±12.3 Cured: 44.5±10	4 medically treated CD 4 medically treated CS 24 remission CD 3 remission CS Average duration of remission:41 months (6-288) *35 healthy controls*	Medically treated: 46.5±32.5 months Cured: 57.6±34.5 months	3T MRI GM/WM boundary was constructed by classifying all white matter voxels in a MRI volume. Cortical thickness estimates were obtained with the shortest distance between the WM and the pial surfaces at each location of the cortex Neuropsychological tests: IGT, RAVLT	Whole brain	Patients showed decreased cortical thickness. Decision making did not correlate with cortical thickness.
LONGITUDINAL								
Khiat, 2000	10‡	0/10	Mean: 41.3 (range 21-64)	5 active CD 5 active CS	NA	1.5T MRI H-MRS Metabolites in ROI were quantified Before and 6 months after correction of hypercortisolism	2 cm3 localized in the thalamic, frontal and temporal area of the left hemisphere	Patients demonstrated recovery of Cho levels in thalamic and frontal areas after correction of hypercortisolism.
Starkman, 1999	18/4**	5/17	38.7±14.8	22 active CD	2.6 ± 2.3 yr	1.5T MRI Manually tracing, volumes within tracing were digitally calculated Before and after surgery (16 ± 9.3 months)	Hippocampus Caudate head ICV	With remission of CD, HFV increased in individual patients up to 10%. This percentage is correlated with the change in UFC.

Table 3. Study characteristics of MRI studies in patients with CS (continued)

Author, year	N	Gender (m/f)	Age mean ± SD	Active/treated	Estimated duration of hypercortisolism	Procedure & Method	Evaluated brain areas	Outcomes
Bourdeau, 2002¥	22	NA	40.9±10.7	14 active CD 8 active CS	NA	CT and/or MRI obtained from routine pituitary evaluation. Measurement of diameters and subjective estimation of degree of cerebral atrophy Before correction of hypercortisolism and after correction (39.7±34.1 months)	Third ventricle Bicaudate Whole brain	After correction of hypercortisolism patients showed a decrease in third ventricle diameter, bicaudate diameter, and subjective evaluation of brain atrophy.
Starkman, 2003	5/19*	4/20	33.7±13.1	24 active CD	2.7 ± 2.1 yr	1.5T MRI Manually tracing, volumes within tracing were digitally calculated Neuropsychological tests: WMS, SRT Psychological assessment: SCL-90-R Before and after surgery (15.7 ± 8.8 months)	Hippocampus Caudate head	Decrease of UFC was correlated with increase of HFV, which was associated with improvement in a learning task.

Table 3. Study characteristics of MRI studies in patients with CS (continued)

Author, year	N	Gender (m/f)	Age mean ± SD	Active/treated	Estimated duration of hypercortisolism	Procedure & Method	Evaluated brain areas	Outcomes
Hook, 2005	5/22*	4/23	38.74±13.24	27 active CD	3.64 ± 3.09 yr	1.5T MRI Manually tracing, volumes within tracing were digitally calculated Volumes were corrected for intracranial volume and controlled for age Neuropsychological tests: SRT, WAIS, Verbal fluency (D) Psychological measures: SCL-90-R Before successful surgical treatment and after (3-5, 6-12, 13-18 months)	Hippocampus Caudate head	Controlling for age, HFV increased from baseline to one-year after treatment, whereas CHV did not increased. Increase in HFV was associated with a decrease in cortisol levels up to one year after treatment.
Merke, 2005¥	11	5/6	12.1±3.4	10 active CD 1 active CS	4.4 ± 1.2 yr	1.5T MRI Manually tracing, volumes were quantified by two independent raters Total cerebral volume was quantified automatically Neuropsychological tests: WISC Psychological assessment: KSADS-PL Before and 1 year after surgery	Cerebrum, ventricles, temporal lobe, hippocampus amygdala	After surgery patients demonstrated an increase of total cerebral brain volume and a decrease in ventricular size. No significant changes were observed in amygdala size or HV.

Table 3. Study characteristics of MRI studies in patients with CS (continued)

Author, year	N	Gender (m/f)	Age mean ± SD	Active/treated	Estimated duration of hypercortisolism	Procedure & Method	Evaluated brain areas	Outcomes
Starkman, 2007	4/19*	4/19	34.0±13.3	23 active CD	2.7 ± 2.1 yr	1.5T MRI Manually tracing, volumes within tracing were digitally calculated Volumes were corrected for intracranial volume Psychological assessment: SCL-90-R Before and approximately one year after surgery	Hippocampus caudate head	Increased HFV and right CHV were associated with lower UFC. Change in right CHV was associated with mood and ideation.
Toffanin, 2011	10	2/8	38.2±13.1	10 active CD	3.5±1.1 yr	1T MRI Manually outlined, volumes were automatically calculated Before and 12 months after surgery	Hippocampus whole brain	Patients demonstrated an increase in right and left hippocampus head volumes after surgery.

* patients from study of Starkman et al. 1999, **patients from study of Starkman et al. 1992, ‡ patients from study of Khiat et al. 1999, ^ patients from study of Resmini et al. 2012, † patients from study of Andela et al. 2013, ¥ cross-sectional and longitudinal design, HV: hippocampal volume, HFV: hippocampal formation volume, CHV: caudate head volume, ICV: intracranial volume, GM: grey matter, WM: white matter, VBM: Voxel-based morphometry, ACC: anterior cingulate cortex, H-MRS: Proton magnetic resonance spectroscopy, Cr: creatine and phosphocreatine, Cho: choline-containing compounds , NAA: N-Acetyl-Aspartate, Glx: Glutamate+Glutamine, QoL: quality of life.

ated with improvement in learning (13;30), but change in CHV was not (13;30). An increase in right caudate volume was associated with improvement in mood (depression, anxiety) and related ideation (obsessive-compulsive and paranoid ideation), whereas change in left CHV and hippocampal volume were not correlated with mood or ideation (21).

Recently, Crespo et al. demonstrated that cortical thickness was not associated with decision making in medically treated eucortisolemic patients and patients in remission (16). Furthermore, in a group of patients with active disease, as well as patients in remission, patients with severe memory impairment showed smaller hippocampal volumes than controls (17), and grey matter volumes of the left lobe of the cerebellum were positively associated with visual memory, and grey matter volumes of the right lobe of the cerebellum were positively associated with reported disease-specific quality of life (19).

In patients with long-term remission reductions in white matter integrity in the left uncinate fasciculus were associated with severity of depressive symptoms, whereas no correlations were found between white matter integrity in other brain regions, grey matter volumes in the ACC and cerebellum, and behavioral outcome (i.e. depressive symptoms, anxiety, apathy, irritability, cognitive failure) (22;29).

DISCUSSION

This systematic review shows that endogenous glucocorticoid excess in Cushing's syndrome has profound effects on the human brain. This includes structural grey matter, possibly white matter abnormalities and neurochemical and functional alterations. After correction of hypercortisolism, the structural and neurochemical alterations improve substantially and correlate with improvements in clinical and behavioral outcomes. Nevertheless, abnormalities in both grey- and white matter are not completely reversible at long-term remission and are accompanied by psychological symptoms and impairments in cognitive functioning (7;22;29;34).

The brain, and in particular the limbic system, is a major target area for cortisol considering the high density of both the mineralo- and glucocorticoid receptor (35). The neurotoxic effects of corticosteroid excess on the central nervous system are well-recognized in experimental animal studies: i.e. reduction of apical dendrites of hippocampal pyramidal neurons (36), hippocampal volume reduction (37), and reduction volume of the left anterior cingulate gyrus (38). Furthermore, experimental models of chronic stress have clearly shown neurotoxic effects that appeared to be reversible by anti-glucocorticoid treatment (39). However, long-term experimental histopathological data after abrogation of corticosteroid overexposure are not available to our knowledge. It is tempting to speculate that the observed psychological morbidity and cognitive impairment in patients with active CS (40;41) could be explained, at least in part, by the findings of MRI studies. In support of this, brain abnormalities and behavioral outcomes are clearly correlated. The anterior cingulate cortex, hippocampus and

amygdala together constitute the neurocircuitry of stress (42). Therefore, psychopathology and cognitive impairment in patients with active CS might be related to structural alterations within this circuitry, but also to alterations in functional activity and connectivity within it. In accordance, changes in functional activity were reported during a facial emotion task in adult patients (25), and a facial memory task in adolescents (26). FMRI studies on other emotional and cognitive tasks (e.g. executive function, memory) in adult patients with CS, or studies assessing functional connectivity during rest, have not been reported. Also, there were no fMRI studies in patients in remission of CS published in the time window of our literature search.

At present, brain characteristics in CS patients who are in long-term remission have been reported in only six cross-sectional MRI studies, with an average duration of remission ranging from 3.4-11.9 years. These studies showed smaller grey matter volumes in the anterior cingulate cortex, larger grey matter volumes in the cerebellum, widespread reductions in white matter integrity (22;29), and alterations in specific neuronal metabolites in the hippocampus (18). The behavioral phenotype of patients in remission of CS (7;34) might also be, at least in part, explained by these findings. This is supported by the observed correlations between reductions in white matter integrity in the left uncinate fasciculus and severity of depressive symptoms in one DTI study. However, no other correlations were identified between the structural brain abnormalities and behavioral outcomes in patients in remission of CS, which might be due to a limited power or to the fact that behavioral outcomes may show stronger associations with functional brain abnormalities (22;29).

The actual course of the residual alterations in patients in long-term remission is hard to capture, since longitudinal studies with long-term follow-up are lacking (i.e. mean duration of follow-up in available studies ranging from 6 to 40 months). Furthermore, previous studies in patients with active CS mainly evaluated the hippocampus, and the first MRI studies in patients with CS did not have access to modern and more sophisticated analytical tools. Therefore, it is plausible to assume that previous studies have been unable to document abnormalities at least in active patients. For instance, white matter integrity as assessed with diffusion tensor imaging (29) has not been evaluated in patients with active disease, which retains us from drawing conclusions about the development of these reductions in white matter integrity.

It is tempting to speculate that the brain abnormalities found in patients with CS during active disease, as well as during remission, also apply for patients with iatrogenic CS due to glucocorticoid treatment. This is supported by findings of similar brain abnormalities in patients while on long-term corticosteroid therapy as in patients with CS (smaller hippocampal, amygdala volumes, cerebral atrophy, alterations in neurochemical concentrations) (43-46).

A considerable amount of between-study heterogeneity was observed. First of all, heterogeneity was present regarding sample composition, with some studies analyzing homogenous groups of patients with pituitary CD or patients with adrenal CS, whereas other studies analyzed a more heterogeneous group of patients with pituitary as well adrenal CS. In addi-

tion, some studies analyzed homogenous groups of patients with active disease or patients in remission, whereas other studies analyzed patients with active, as well as patients with remitted disease. Secondly, studies demonstrated a great variety in analyzed brain regions of interest and in the methodology used. Consequently, no meta-analysis could be performed. Furthermore, it should be acknowledged that CS is associated with multisystem morbidity (47) and pituitary hormone deficiencies, which all can affect the brain (48-52).

In conclusion, patients with CS demonstrate structural brain abnormalities, as well as neurochemical and functional abnormalities, which only partly recover during long-term remission, since these still occur even after long-term remission. Cushing's syndrome might be considered as a human model of nature that provides a keyhole perspective of the neurotoxic effects of exogenous glucocorticoids on the brain.

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SUPPLEMENT 1. SEARCH STRATEGY

PubMed (1 query):

("cushing disease"[All Fields] OR "cushing's disease"[All Fields] OR "cushings disease"[All Fields] OR "Cushing Syndrome"[Mesh] OR "Cushing's Syndrome"[all fields] OR "Cushing Syndrome"[all fields] OR "Cushings Syndrome"[all fields] OR "cushing"[tiab] OR "cushings"[tiab] OR "cushing's"[tiab] OR "ACTH-Secreting Pituitary Adenoma"[Mesh] OR "ACTH-Producing Pituitary Adenoma"[all fields] OR "ACTH Producing Pituitary Adenoma" OR "ACTH-Producing Pituitary Adenomas"[all fields] OR "ACTH Producing Pituitary Adenomas"[all fields] OR "ACTH Secreting Pituitary Adenoma"[all fields] OR "ACTH-Secreting Pituitary Adenomas"[all fields] OR "ACTH-Secreting Pituitary Adenoma"[all fields] OR "ACTH Secreting Pituitary Adenomas"[all fields]) AND ("functional mri"[All Fields] OR "fMRI"[all fields] OR "fmr"[all fields] OR "f mr"[all fields] OR "functional magnetic"[all fields] OR "functional mr"[all fields] OR (("Magnetic Resonance Imaging"[Mesh] OR "mri"[All Fields] OR "MRIs"[All Fields] OR "magnetic resonance imaging"[all fields]) AND ("functional"[all fields] OR "Mental Processes"[Mesh] OR "cognition"[all fields] OR "cognitive"[all fields] OR "task"[all fields] OR "tasks"[all fields] OR "learning"[all fields] OR "memory"[all fields]))) AND ("brain"[all fields] OR "Brain"[Mesh] OR "hippocampus"[all fields] OR "hippocampal"[all fields] OR "hippocampi"[all fields] OR hippocamp*[all fields] OR "amygdala"[all fields] OR "amygdalae"[all fields] OR "lymbic system"[all fields] OR "cerebellar"[all fields] OR "cerebellum"[all fields] OR cerebel*[all fields] OR cerebr*[all fields] OR "grey matter"[all fields] OR "gray matter"[all fields] OR "Mesencephalon"[all fields] OR "Locus Coeruleus"[all fields] OR "Raphe Nuclei"[all fields] OR "Tectum Mesencephali"[all fields] OR "Inferior Colliculi"[all fields] OR "Superior Colliculi"[all fields] OR "Tegmentum Mesencephali"[all fields] OR "Cerebral Aqueduct"[all fields] OR "Pedunculopontine Tegmental Nucleus"[all fields] OR "Periaqueductal Gray"[all fields] OR "Red Nucleus"[all fields] OR "Substantia Nigra"[all fields] OR "Ventral Tegmental Area"[all fields] OR "Reticular Formation"[all fields] OR "Rhombencephalon"[all fields] OR "Medulla Oblongata"[all fields] OR "Area Postrema"[all fields] OR "Olivary Nucleus"[all fields] OR "Solitary Nucleus"[all fields] OR "Metencephalon"[all fields] OR "Cerebellum"[all fields] OR "Cerebellar Cortex"[all fields] OR "Purkinje Cells"[all fields] OR "Cerebellar Nuclei"[all fields] OR "Cerebellopontine Angle"[all fields] OR "Pons"[all fields] OR "Cochlear Nucleus"[all fields] OR "Locus Coeruleus"[all fields] OR "Vestibular Nuclei"[all fields] OR "Raphe Nuclei"[all fields] OR "Trigeminal Nuclei"[all fields] OR "Trigeminal Nucleus"[all fields] OR "Trigeminal Caudal Nucleus"[all fields] OR "Cerebral"[all fields] OR "Choroid Plexus"[all fields] OR "Ependyma"[all fields] OR "Fourth Ventricle"[all fields] OR "Lateral Ventricles"[all fields] OR "Septum Pellucidum"[all fields] OR "Third Ventricle"[all fields] OR "Limbic System"[all fields] OR "Amygdala"[all fields] OR "Epithalamus"[all fields] OR "Habenula"[all fields] OR "Pineal Gland"[all fields] OR "Gyrus Cinguli"[all fields] OR "Dentate Gyrus"[all fields] OR "Pyramidal Cells"[all fields] OR "Hypothalamus"[all fields] OR "Olfactory Pathways"[all fields] OR "Islands of Calleja"[all fields] OR "Olfactory Bulb"[all fields] OR "Parahippocampal Gyrus"[all fields] OR "Entorhinal Cortex"[all fields] OR "Perforant Pathway"[all fields] OR "Substantia Innominata"[all fields] OR "Mesencephalon"[all fields] OR "Locus Coeruleus"[all fields] OR "Raphe Nuclei"[all fields] OR "Tectum Mesencephali"[all fields] OR "Inferior Colliculi"[all fields] OR "Superior Colliculi"[all fields] OR "Tegmentum Mesencephali"[all fields] OR "Cerebral Aqueduct"[all fields] OR "Pedunculopontine Tegmental Nucleus"[all fields] OR "Periaqueductal Gray"[all fields] OR "Red Nucleus"[all fields] OR "Substantia Nigra"[all fields] OR "Ventral Tegmental Area"[all fields] OR "Prosencephalon"[all fields] OR "Diencephalon"[all fields] OR "Epithalamus"[all fields] OR "Habenula"[all fields] OR "Pineal Gland"[all fields] OR "Hypothalamus"[all fields] OR "Hypothalamic"[all fields] OR "Subthalamus"[all fields] OR "Entopeduncular Nucleus"[all fields] OR "Subthalamic Nucleus"[all fields] OR "Thalamus"[all fields] OR "Thalamic Nuclei"[all fields] OR "Septal Nuclei"[all fields] OR "Septum Pellucidum"[all fields] OR "Telencephalon"[all fields] OR "Cerebrum"[all fields] OR "Basal Ganglia"[all fields] OR "Cerebral Cortex"[all fields] OR "Corpus Callosum"[all fields] OR "Diagonal Band of Broca"[all fields] OR "Internal Capsule"[all fields] OR "Olfactory Pathways"[all fields] OR "Islands of Calleja"[all fields] OR "Olfactory Bulb"[all fields] OR "Septum of Brain"[all fields] OR "Septal Nuclei"[all fields] OR "Septum Pellucidum"[all fields] OR "Rhombencephalon"[all fields] OR "Amygdala"[all fields] OR "Corpus Striatum"[all fields] OR "Globus Pallidus"[all fields] OR "Neostriatum"[all fields] OR "Nucleus Accumbens"[all fields] OR "Substantia Innominata"[all fields] OR "Basal Nucleus of Meynert"[all fields] OR "Caudate Nucleus"[all fields] OR "High Vocal Center"[all fields] OR "Putamen"[all fields] OR "Frontal Lobe"[all fields] OR "Motor Cortex"[all fields] OR "Prefrontal Cortex"[all fields] OR "Hippocampus"[all fields] OR "Dentate Gyrus"[all fields] OR "Pyramidal Cells"[all fields] OR "Neocortex"[all fields] OR "Occipital Lobe"[all fields] OR "Visual Cortex"[all fields] OR "Parietal Lobe"[all fields] OR "Somatosensory Cortex"[all fields] OR "Pyramidal Cells"[all fields] OR "Temporal Lobe"[all fields] OR "Auditory Cortex"[all fields] OR "Parahippocampal Gyrus"[all fields] OR "Entorhinal Cortex"[all fields] OR "Metencephalon"[all fields] OR "Myelencephalon"[all

fields] OR "Raphe Nuclei"[all fields] OR "Medulla Oblongata"[all fields] OR "Area Postrema"[all fields] OR "Olivary Nucleus"[all fields] OR "Solitary Nucleus"[all fields] OR "white matter"[all fields])
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1: (cushing disease/ OR cushing syndrome/ OR "cushing disease".mp OR "cushing's disease".mp OR "cushings disease".mp OR "Cushing's Syndrome".mp OR "Cushing Syndrome".mp OR "Cushings Syndrome".mp OR "cushing".mp OR "cushings".mp OR "cushing's".mp OR ACTH secreting adenoma/ OR "ACTH-Producing Pituitary Adenoma".mp OR "ACTH Producing Pituitary Adenoma".mp OR "ACTH-Producing Pituitary Adenomas".mp OR "ACTH Producing Pituitary Adenomas".mp OR "ACTH Secreting Pituitary Adenoma".mp OR "ACTH-Secreting Pituitary Adenomas".mp OR "ACTH-Secreting Pituitary Adenoma".mp OR "ACTH Secreting Pituitary Adenomas".mp) AND (functional magnetic resonance imaging/ OR "functional mri".mp OR "fMRI".mp OR "fmr".mp OR "f mr".mp OR "functional magnetic".mp OR "functional mr".mp OR ((exp nuclear magnetic resonance imaging/ OR "mri".mp OR "MRIs".mp OR "magnetic resonance imaging".mp) AND ("functional".mp OR exp mental function/ OR "cognition".mp OR "cognitive".mp OR "task".mp OR "tasks".mp OR "learning".mp OR "memory".mp))) AND ("brain".mp OR exp Brain/ OR "hippocampus".mp OR "hippocampal".mp OR "hippocampi".mp OR hippocamp*.mp OR "amygdala".mp OR "amygdalae".mp OR "lymbic system".mp OR "cerebellar".mp OR "cerebellum".mp OR cerebel*.mp OR cerebr*.mp OR "grey matter".mp OR "gray matter".mp OR "Mesencephalon".mp OR "Locus Coeruleus".mp OR "Raphe Nuclei".mp OR "Tectum Mesencephali".mp OR "Inferior Colliculi".mp OR "Superior Colliculi".mp OR "Tegmentum Mesencephali".mp OR "Cerebral Aqueduct".mp OR "Pedunculopontine Tegmental Nucleus".mp OR "Periaqueductal Gray".mp OR "Red Nucleus".mp OR "Substantia Nigra".mp OR "Ventral Tegmental Area".mp OR "Reticular Formation".mp OR "Rhombencephalon".mp OR "Medulla Oblongata".mp OR "Area Postrema".mp OR "Olivary Nucleus".mp OR "Solitary Nucleus".mp OR "Metencephalon".mp OR "Cerebellum".mp OR "Cerebellar Cortex".mp OR "Purkinje Cells".mp OR "Cerebellar Nuclei".mp OR "Cerebellopontine Angle".mp OR "Pons".mp OR "Cochlear Nucleus".mp OR "Locus Coeruleus".mp OR "Vestibular Nuclei".mp OR "Raphe Nuclei".mp OR "Trigeminal Nuclei".mp OR "Trigeminal Nucleus".mp OR "Trigeminal Caudal Nucleus".mp OR "Cerebral".mp OR "Choroid Plexus".mp OR "Ependyma".mp OR "Fourth Ventricle".mp OR "Lateral Ventricles".mp OR "Septum Pellucidum".mp OR "Third Ventricle".mp OR "Limbic System".mp OR "Amygdala".mp OR "Epithalamus".mp OR "Habenula".mp OR "Pineal Gland".mp OR "Gyrus Cinguli".mp OR "Dentate Gyrus".mp OR "Pyramidal Cells".mp OR "Hypothalamus".mp OR "Olfactory Pathways".mp OR "Islands of Calleja".mp OR "Olfactory Bulb".mp OR "Parahippocampal Gyrus".mp OR "Entorhinal Cortex".mp OR "Perforant Pathway".mp OR "Substantia Innominata".mp OR "Mesencephalon".mp OR "Locus Coeruleus".mp OR "Raphe Nuclei".mp OR "Tectum Mesencephali".mp OR "Inferior Colliculi".mp OR "Superior Colliculi".mp OR "Tegmentum Mesencephali".mp OR "Cerebral Aqueduct".mp OR "Pedunculopontine Tegmental Nucleus".mp OR "Periaqueductal Gray".mp OR "Red Nucleus".mp OR "Substantia Nigra".mp OR "Ventral Tegmental Area".mp OR "Prosencephalon".mp OR "Diencephalon".mp OR "Epithalamus".mp OR "Habenula".mp OR "Pineal Gland".mp OR "Hypothalamus".mp OR "Hypothalamic".mp OR "Subthalamus".mp OR "Entopeduncular Nucleus".mp OR "Subthalamic Nucleus".mp OR "Thalamus".mp OR "Thalamic Nuclei".mp OR "Septal Nuclei".mp OR "Septum Pellucidum".mp OR "Telencephalon".mp OR "Cerebrum".mp OR "Basal Ganglia".mp OR "Cerebral Cortex".mp OR "Corpus Callosum".mp OR "Diagonal Band of Broca".mp OR "Internal Capsule".mp OR "Olfactory Pathways".mp OR "Islands of Calleja".mp OR "Olfactory Bulb".mp OR "Septum of Brain".mp OR "Septal Nuclei".mp OR "Septum Pellucidum".mp OR "Rhombencephalon".mp OR "Amygdala".mp OR "Corpus Striatum".mp OR "Globus Pallidus".mp OR "Neostriatum".mp OR "Nucleus Accumbens".mp OR "Substantia Innominata".mp OR "Basal Nucleus of Meynert".mp OR "Caudate Nucleus".mp OR "High Vocal Center".mp OR "Putamen".mp OR "Frontal Lobe".mp OR "Motor Cortex".mp OR "Prefrontal Cortex".mp OR "Hippocampus".mp OR "Dentate Gyrus".mp OR "Pyramidal Cells".mp OR "Neocortex".mp OR "Occipital Lobe".mp OR "Visual Cortex".mp OR "Parietal Lobe".mp OR "Somatosensory Cortex".mp OR "Pyramidal Cells".mp OR "Temporal Lobe".mp OR "Auditory Cortex".mp OR "Parahippocampal Gyrus".mp OR "Entorhinal Cortex".mp OR "Metencephalon".mp OR "Myelencephalon".mp OR "Raphe Nuclei".mp OR "Medulla Oblongata".mp OR "Area Postrema".mp OR "Olivary Nucleus".mp OR "Solitary Nucleus".mp OR "white matter".mp)
2: (cushing disease/ OR cushing syndrome/ OR "cushing disease".mp OR "cushing's disease".mp OR "cushings disease".mp OR "Cushing's Syndrome".mp OR "Cushing Syndrome".mp OR "Cushings Syndrome".mp OR "cushing".mp OR "cushings".mp OR "cushing's".mp OR ACTH secreting adenoma/ OR "ACTH-Producing Pituitary Adenoma".mp OR "ACTH Producing Pituitary Adenoma" OR "ACTH-Producing Pituitary Adenomas".mp OR "ACTH Producing Pituitary Adenomas".mp OR "ACTH Secreting Pituitary Adenoma".mp OR "ACTH-Secreting Pituitary Adenomas".mp OR "ACTH-Secreting Pituitary Adenoma".mp OR "ACTH Secreting Pituitary Adenomas".mp) AND (functional magnetic

resonance imaging/ OR "functional mri".mp OR "fMRI".mp OR "fmr".mp OR "f mr".mp OR "functional magnetic".mp OR "functional mr".mp)

Web of Science (2 queries):

1: TS=((cushing disease OR cushing syndrome OR "cushing disease" OR "cushing's disease" OR "cushings disease" OR "Cushing's Syndrome" OR "Cushing Syndrome" OR "Cushings Syndrome" OR "cushing" OR "cushings" OR "cushing's" OR ACTH secreting adenoma OR "ACTH-Producing Pituitary Adenoma" OR "ACTH Producing Pituitary Adenoma" OR "ACTH-Producing Pituitary Adenomas" OR "ACTH Producing Pituitary Adenomas" OR "ACTH Secreting Pituitary Adenoma" OR "ACTH-Secreting Pituitary Adenomas" OR "ACTH-Secreting Pituitary Adenoma" OR "ACTH Secreting Pituitary Adenomas") AND (functional magnetic resonance imaging OR "functional mri" OR "fMRI" OR "fmr" OR "f mr" OR "functional magnetic" OR "functional mr" OR ((nuclear magnetic resonance imaging OR "mri" OR "MRIs" OR "magnetic resonance imaging") AND ("functional" OR mental function OR "cognition" OR "cognitive" OR "task" OR "tasks" OR "learning" OR "memory"))) AND ("brain" OR Brain OR "hippocampus" OR "hippocampal" OR "hippocampi" OR hippocamp* OR "amygdala" OR "amygdalae" OR "lymbic system" OR "cerebellar" OR "cerebellum" OR cerebel* OR cerebr* OR "grey matter" OR "gray matter" OR "Mesencephalon" OR "Locus Coeruleus" OR "Raphe Nuclei" OR "Tectum Mesencephali" OR "Inferior Colliculi" OR "Superior Colliculi" OR "Tegmentum Mesencephali" OR "Cerebral Aqueduct" OR "Pedunculopontine Tegmental Nucleus" OR "Periaqueductal Gray" OR "Red Nucleus" OR "Substantia Nigra" OR "Ventral Tegmental Area" OR "Reticular Formation" OR "Rhombencephalon" OR "Medulla Oblongata" OR "Area Postrema" OR "Olivary Nucleus" OR "Solitary Nucleus" OR "Metencephalon" OR "Cerebellum" OR "Cerebellar Cortex" OR "Purkinje Cells" OR "Cerebellar Nuclei" OR "Cerebellopontine Angle" OR "Pons" OR "Cochlear Nucleus" OR "Locus Coeruleus" OR "Vestibular Nuclei" OR "Raphe Nuclei" OR "Trigeminal Nuclei" OR "Trigeminal Nucleus" OR "Trigeminal Caudal Nucleus" OR "Cerebral" OR "Choroid Plexus" OR "Ependyma" OR "Fourth Ventricle" OR "Lateral Ventricles" OR "Septum Pellucidum" OR "Third Ventricle" OR "Limbic System" OR "Amygdala" OR "Epithalamus" OR "Habenula" OR "Pineal Gland" OR "Gyrus Cinguli" OR "Dentate Gyrus" OR "Pyramidal Cells" OR "Hypothalamus" OR "Olfactory Pathways" OR "Islands of Calleja" OR "Olfactory Bulb" OR "Parahippocampal Gyrus" OR "Entorhinal Cortex" OR "Perforant Pathway" OR "Substantia Innominata" OR "Mesencephalon" OR "Locus Coeruleus" OR "Raphe Nuclei" OR "Tectum Mesencephali" OR "Inferior Colliculi" OR "Superior Colliculi" OR "Tegmentum Mesencephali" OR "Cerebral Aqueduct" OR "Pedunculopontine Tegmental Nucleus" OR "Periaqueductal Gray" OR "Red Nucleus" OR "Substantia Nigra" OR "Ventral Tegmental Area" OR "Prosencephalon" OR "Diencephalon" OR "Epithalamus" OR "Habenula" OR "Pineal Gland" OR "Hypothalamus" OR "Hypothalamic" OR "Subthalamus" OR "Entopeduncular Nucleus" OR "Subthalamic Nucleus" OR "Thalamus" OR "Thalamic Nuclei" OR "Septal Nuclei" OR "Septum Pellucidum" OR "Telencephalon" OR "Cerebrum" OR "Basal Ganglia" OR "Cerebral Cortex" OR "Corpus Callosum" OR "Diagonal Band of Broca" OR "Internal Capsule" OR "Olfactory Pathways" OR "Islands of Calleja" OR "Olfactory Bulb" OR "Septum of Brain" OR "Septal Nuclei" OR "Septum Pellucidum" OR "Rhombencephalon" OR "Amygdala" OR "Corpus Striatum" OR "Globus Pallidus" OR "Neostriatum" OR "Nucleus Accumbens" OR "Substantia Innominata" OR "Basal Nucleus of Meynert" OR "Caudate Nucleus" OR "High Vocal Center" OR "Putamen" OR "Frontal Lobe" OR "Motor Cortex" OR "Prefrontal Cortex" OR "Hippocampus" OR "Dentate Gyrus" OR "Pyramidal Cells" OR "Neocortex" OR "Occipital Lobe" OR "Visual Cortex" OR "Parietal Lobe" OR "Somatosensory Cortex" OR "Pyramidal Cells" OR "Temporal Lobe" OR "Auditory Cortex" OR "Parahippocampal Gyrus" OR "Entorhinal Cortex" OR "Metencephalon" OR "Myelencephalon" OR "Raphe Nuclei" OR "Medulla Oblongata" OR "Area Postrema" OR "Olivary Nucleus" OR "Solitary Nucleus" OR "white matter"))

2: TS=(("cushing disease" OR "cushing syndrome" OR chsing OR cushing* OR "cushing disease" OR "cushing's disease" OR "cushings disease" OR "Cushing's Syndrome" OR "Cushing Syndrome" OR "Cushings Syndrome" OR "cushing" OR "cushings" OR "cushing's" OR ACTH secreting adenoma OR "ACTH-Producing Pituitary Adenoma" OR "ACTH Producing Pituitary Adenoma" OR "ACTH-Producing Pituitary Adenomas" OR "ACTH Producing Pituitary Adenomas" OR "ACTH Secreting Pituitary Adenoma" OR "ACTH-Secreting Pituitary Adenomas" OR "ACTH-Secreting Pituitary Adenoma" OR "ACTH Secreting Pituitary Adenomas") AND ("functional magnetic" OR "functional mri" OR "fMRI" OR "fmr" OR "f mr" OR "functional magnetic" OR "functional mr" OR "functional imaging"))

Cochrane (1 query):

((cushing disease OR cushing syndrome OR cushing disease OR cushing's disease OR cushings disease OR Cushing's Syndrome OR Cushing Syndrome OR Cushings Syndrome OR cushing OR cushings OR cushing's OR ACTH secreting adenoma OR ACTH-Producing Pituitary Adenoma OR ACTH Producing Pituitary Adenoma OR ACTH-Producing Pituitary Adenomas OR ACTH Producing Pituitary Adenomas OR ACTH Secreting Pituitary Adenoma OR ACTH-Secreting Pituitary Adenomas OR ACTH-Secreting Pituitary Adenoma OR ACTH Secreting Pituitary Ad-

enomas) AND (functional magnetic resonance imaging OR functional mri OR fMRI OR fmr OR f mr OR functional magnetic OR functional mr OR ((nuclear magnetic resonance imaging OR mri OR MRIs OR magnetic resonance imaging) AND (functional OR mental function OR cognition OR cognitive OR task OR tasks OR learning OR memory))) AND (brain OR Brain OR hippocampus OR hippocampal OR hippocampi OR hippocamp* OR amygdala OR amygdalae OR lymbic system OR cerebellar OR cerebellum OR cerebel* OR cerebr* OR grey matter OR gray matter OR Mesencephalon OR Locus Coeruleus OR Raphe Nuclei OR Tectum Mesencephali OR Inferior Colliculi OR Superior Colliculi OR Tegmentum Mesencephali OR Cerebral Aqueduct OR Pedunculopontine Tegmental Nucleus OR Periaqueductal Gray OR Red Nucleus OR Substantia Nigra OR Ventral Tegmental Area OR Reticular Formation OR Rhombencephalon OR Medulla Oblongata OR Area Postrema OR Olivary Nucleus OR Solitary Nucleus OR Metencephalon OR Cerebellum OR Cerebellar Cortex OR Purkinje Cells OR Cerebellar Nuclei OR Cerebellopontine Angle OR Pons OR Cochlear Nucleus OR Locus Coeruleus OR Vestibular Nuclei OR Raphe Nuclei OR Trigeminal Nuclei OR Trigeminal Nucleus OR Trigeminal Caudal Nucleus OR Cerebral OR Choroid Plexus OR Ependyma OR Fourth Ventricle OR Lateral Ventricles OR Septum Pellucidum OR Third Ventricle OR Limbic System OR Amygdala OR Epithalamus OR Habenula OR Pineal Gland OR Gyrus Cinguli OR Dentate Gyrus OR Pyramidal Cells OR Hypothalamus OR Olfactory Pathways OR Islands of Calleja OR Olfactory Bulb OR Parahippocampal Gyrus OR Entorhinal Cortex OR Perforant Pathway OR Substantia Innominata OR Mesencephalon OR Locus Coeruleus OR Raphe Nuclei OR Tectum Mesencephali OR Inferior Colliculi OR Superior Colliculi OR Tegmentum Mesencephali OR Cerebral Aqueduct OR Pedunculopontine Tegmental Nucleus OR Periaqueductal Gray OR Red Nucleus OR Substantia Nigra OR Ventral Tegmental Area OR Prosencephalon OR Diencephalon OR Epithalamus OR Habenula OR Pineal Gland OR Hypothalamus OR Hypothalamic OR Subthalamus OR Entopeduncular Nucleus OR Subthalamic Nucleus OR Thalamus OR Thalamic Nuclei OR Septal Nuclei OR Septum Pellucidum OR Telencephalon OR Cerebrum OR Basal Ganglia OR Cerebral Cortex OR Corpus Callosum OR Diagonal Band of Broca OR Internal Capsule OR Olfactory Pathways OR Islands of Calleja OR Olfactory Bulb OR Septum of Brain OR Septal Nuclei OR Septum Pellucidum OR Rhombencephalon OR Amygdala OR Corpus Striatum OR Globus Pallidus OR Neostriatum OR Nucleus Accumbens OR Substantia Innominata OR Basal Nucleus of Meynert OR Caudate Nucleus OR High Vocal Center OR Putamen OR Frontal Lobe OR Motor Cortex OR Prefrontal Cortex OR Hippocampus OR Dentate Gyrus OR Pyramidal Cells OR Neocortex OR Occipital Lobe OR Visual Cortex OR Parietal Lobe OR Somatosensory Cortex OR Pyramidal Cells OR Temporal Lobe OR Auditory Cortex OR Parahippocampal Gyrus OR Entorhinal Cortex OR Metencephalon OR Myelencephalon OR Raphe Nuclei OR Medulla Oblongata OR Area Postrema OR Olivary Nucleus OR Solitary Nucleus OR white matter))

SUPPLEMENT 2. EXPLANATION OF USED METHODS

Method	Explanation
Imaging techniques	
Functional MRI (fMRI)	Functional neuroimaging procedure measuring brain activity by detecting changes in blood flow and oxygen response (BOLD response).
Face Memory Task	Consists of two phases encoding of facial emotional expression within the scanner, and the surprise recognition after the scan.
Facial Emotion Perception Test (FEPT)	Assesses accuracy and speed of identification of facial expressions, with categorization of animals used as a control for visual processing ability and fine motor speed. Participants are asked to categorize faces into four categories (happy, sag, fearful, angry) and animals into four categories (dogs, cats, primates, birds) outside the scanner and within the scanner.
Proton Magnetic Resonance Spectroscopy (H-MRS)	Analytical technique that uses signals from hydrogen protons to determine the relative concentrations of target brain metabolites.
Neuropsychological test	
Rey Auditory Verbal Learning Test (RAVLT)	Evaluates verbal learning and memory and consists of 15 words which are visually presented in three trials and a fourth delayed trial. The amount of words recalled after each trial is counted. The more words produced, the better the learning capability.
Rey-Osterrieth Complex Figure (ROCF)	Assesses visual memory. Participants are asked to copy the figure, and draw it *immediately* or after 3 minutes (depending on the test version), and after 20 minutes again without seeing the figure.
Wisconsin Card Sorting Test (WCST)	Assesses cognitive flexibility. Four models are shown to participants. Participants are asked to match their cards with one of the model, aiming to find the correct criteria, while criteria change over time.
Grooved Pegboard (GP)	Assesses fine motor skills. Participants are asked to insert some pegs in a pegboard, as quick as possible, with both the dominant and non-dominant hand.
Iowa Gambling Task (IGT)	Assesses decision making. Participants see four cards (A, B, C, D) on a computer screen. A-B are considered riskier, but subjects win more money on the short-term, but lose more in the long-term. C-D are considered safer, but subjects win less money in the short-term, but lose less money in the long-term. An increase in both the amount of lost money and the number of riskier cards reflect poorer decision making.
Selective Reminding Task (SRT)	Consists of a six-trial word-list learning task of unpaired words. After the first trial participants are asked to state the words they remembered, without regard to order. In the five next trials, after being asked to state all 12 words, participants were selectively reminded only the words they did not remember from the previous trial.
Trail Making Test A (TMT-A)	Assesses motor functions. Participants are asked to connect numbers in the right order.

Trail Making Test B (TMT-B)	Assesses dived attention. Participants are asked to connect numbers and letters in ascending order.
Wechsler Intelligence Scale for Children (WISC)	Measures intelligence in children aged 6-16 years.
Wechsler Adult Intelligence Scale (WAIS)	Measures intelligence in adults and older adolescents.
Boston Naming Test (BNT)	Assesses denomination. Participants are asked to name a picture.
Symbol Digit Modality Test (SDMT)	Assesses information processing speeds (attention, visual scanning, tracking). A model with symbols and numbers are shown to participants. In the presence of these models, participants are asked to fill out the numbers at the corresponding symbols, as quickly as possible.
Verbal fluency - FAS	Assesses phonetic fluency. Participants are asked to call all the words they can within one minute. Words should begin with a specific letter, i.e. F-A-S.
Verbal fluency (D)	Assesses phonetic fluency. Participants are asked to call all the words they can within one minute beginning with letter "D".
California Verbal Learning Test – Children (CVLT-C)	Assess learning and recall abilities as well as verbal learning and memory deficits.
Woodcock-Johnson Psychoeducational Battery Revised: Test of Achievement	Assesses cognitive abilities, scholastic aptitude, and achievement in the areas of reading, mathematics, and written language.
Cognitive Failure Questionnaire (CFQ)	Assesses ones failures in perception, memory, and motor function. On this 25-item questionnaire each question can be answered on a 5-point Likert scale. A higher sum score indicates that an individual experiences greater cognitive failure.
Physical questionnaires	
Physical and Neurologic Examination of Subtle Signs (PANESS)	Assesses subtle deficits of gross and fine motor function.
Cushing Severity Index (CSI)	Assesses severity of symptoms and to retrospectively estimate (clinical severity) at the time of active disease. It contains eight clinical features and can be scored on a 3-point scale. A higher score indicates greater severity.
Psychological measures	
Beck Depression Inventory (BDI)	21-item inventory measuring severity of depression. Each question is scored on a scale from 0 to 3. Total higher scores indicate more severe depressive symptoms.
State-Trait Anxiety Inventory (STAI)	40-item inventory measuring state anxiety and trait anxiety. Higher scores indicate higher levels of anxiety.
Montgomery-Asberg Depression Rating Scale (MADRS)	10-item questionnaire which focuses on the most commonly occurring symptoms of depressive illness (i.e. apparent sadness, reported sadness, inability to feel, difficulty in concentration, inner tension, pessimistic thoughts, suicidal thoughts, lassitude, reduced sleep, reduced appetite). A higher total score indicates more severe depression.
Inventory of Depression Symptomatology (IDS)	28-item multiple-choice questionnaire, which is designed to measure severity of depressive symptoms. A higher total score indicates greater severity of depressive symptoms.

Beck Anxiety Inventory (BAI)	21-item inventory which evaluates anxiety. Each question can be answered on a 4-point Likert scale. A higher sum score indicates greater severity of anxiety.
Fear Questionnaire (FQ)	24-item questionnaire assessing phobic anxiety. Each question can be answered on an 8-point Likert scale. This total phobia score can be divided into three subscales: the agoraphobia subscale, the blood injury phobia subscale and the social phobia subscale. Higher scores indicate greater severity of phobias.
Irritability Scale (IS)	Consists of 14 items on a 4-point scale, with higher scores indicating greater irritability. A total score of 14 point or more is being used to characterize subjects as irritable.
Apathy Scale (AS)	Consists of 14 questions on a 4-point scale, with higher scores indicating greater apathy. A total score of 14 points or more is being used to characterize subjects as apathetic.
Symptom Checklist (SCL-90-R)	Consists of 90 items and assesses physical and psychological complaints.
Behavioral Assessment System for Children (BASC)	Multidimensional system used to evaluate the behavior and self-perceptions of children, adolescents and young adults.
Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (KSADS-PL)	Semi-structured interview designed to generate DSM-IV psychiatric diagnoses in children of 6-18 years.
Quality of Life	
CushingQoL	Assess Cushing-related QoL and consists of 12 questions on a 5-point Likert scale ranging from always to never, with a lower score indicating a greater impact on QoL.

CHAPTER 3

Smaller grey matter volumes in the anterior cingulate cortex and greater cerebellar volumes in patients with long-term remission of Cushing's disease: a case-control study

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ABSTRACT

Objective: Patients with long-term remission of Cushing's disease (CD) have persistent psychological and cognitive impairments. It is unknown whether, and to what extent, these impairments are accompanied by structural abnormalities in the brain. We aim to investigate structural changes in the brain in a sample of patients with predominantly long-term remission of CD and to examine whether these changes are associated with psychological and cognitive dysfunction, and clinical severity.

Design: A cross-sectional, case control study.

Methods: In 25 patients with predominantly long-term remission of CD and 25 matched healthy controls, grey matter volumes in the regions of interest (hippocampus, amygdala, anterior cingulate cortex) and in the whole brain were examined, using 3T Magnetic Resonance Imaging and a voxel-based morphometry approach. Psychological and cognitive functioning were assessed using validated questionnaires and clinical severity was assessed using the Cushing's syndrome Severity Index.

Results: Compared to controls, patients had smaller grey matter volumes of areas in the anterior cingulate cortex (on average 14%, $P<0.05$) and greater volume of the left posterior lobe of the cerebellum (on average 34%, $P<0.05$). As expected, patients with remitted CD reported more depressive symptoms ($P=0.005$), more anxiety ($P=0.003$), more social phobia ($P=0.034$), more apathy ($P=0.002$) and more cognitive failure ($P=0.023$) compared to controls, but the differences in grey matter volumes were not associated with psychological or cognitive measures, nor with clinical severity.

Conclusion: Patients with predominantly long-term remission of CD showed specific structural brain abnormalities, in the presence of psychological dysfunction. Our data form a basis for future work aimed at elucidating the relation of the structural brain abnormalities and the sustained psychological deficits after long-term exposure to high cortisol levels.

INTRODUCTION

Cushing's disease (CD) is caused by excessive endogenous cortisol exposure (1). After successful surgical correction of hypercortisolism, the physical, psychological and cognitive symptoms improve substantially (2;3). However, despite curative treatment of the adenomas *per se*, multiple physical, psychological and cognitive complaints may persist and morbidity and mortality remain increased, even in case of long-term remission (4;5).

Cortisol is the main hormonal mediator of the stress response and acts via stimulation of both the mineralocorticoid (MR) and glucocorticoid receptors (GR) in the central nervous system. HPA-axis activity is regulated by limbic structures such as the hippocampus and amygdala and the anterior cingulate cortex (ACC) (6). These areas are also important target areas for glucocorticoid hormones via activation of MR and GR. In accordance, long-term exposure to elevated cortisol levels has been linked to functional and structural changes of these limbic structures both in humans and preclinical studies (7;8). For example, prolonged cortisol elevations predict memory dysfunction and reduced volume of the hippocampus and ACC during aging (9;10). Moreover, in patients with Cushing's syndrome, hypercortisolism was associated with smaller hippocampal volumes and overall brain atrophy (11-13), with increasing hippocampal volumes and improving emotional and cognitive functioning after correction of hypercortisolism (11;14-18).

To date, the long-term effects of chronic overexposure to cortisol, such as in CD, on the brain has been evaluated in only one study (19). In that study, focusing on memory function and hippocampal volume in 33 patients with Cushing's syndrome and 34 matched healthy controls, no overall differences in hippocampal volume between patients and controls were found (19). However, there was a considerable heterogeneity within the patient group in terms of disease status and treatment. Both patients with active CD and patients with CD in remission, with either pituitary or adrenal disease, were included and analyzed as one group (19), precluding definite conclusions. Furthermore, volumetric analyses were limited to the hippocampus and did not include other brain regions known to be important in emotional and cognitive functioning.

Recently, we performed a large cross-sectional study in a well-characterized cohort of patients with long-term biochemical remission, i.e. successful treatment for CD. We found a decreased quality of life (20;21), a higher prevalence of psychopathology (e.g. depression, anxiety, apathy) (22), maladaptive personality traits (22) and subtle cognitive impairments (23) despite long-term cure. The results of these studies suggest irreversible effects of longer periods with glucocorticoid excess on brain function and possibly brain structure. These findings were associated with clinical characteristics (e.g. hydrocortisone dependency).

The primary aim of the present cross-sectional study was to investigate whether this cohort of patients with predominantly long-term biochemical remission of pituitary-dependent CD shows structural brain abnormalities, using a voxel-based morphometry approach. In particular, given the results of our previous study, we aimed to evaluate structural changes in

important cerebral regions of the limbic system, i.e. the hippocampus, the amygdala, but also in a cerebral key region for both cognitive and emotional functioning: the ACC. Furthermore, we performed an explorative whole brain analysis to detect possible structural changes in areas outside this *a priori* defined regions of interest. In addition, we aimed to explore associations between structural changes and measures of psychological and cognitive dysfunction and to take clinical characteristics, such as hydrocortisone dependency into account.

SUBJECTS AND METHODS

Subjects

All patients in long-term remission of CD of pituitary origin monitored at our institute (N=49) and between 18 and 60 years of age, were invited by letter and those who did not respond were contacted by phone. The response rate was 96% and 31 patients were screened for eligibility. Exclusion criteria were (history of) drug- or alcohol abuse, neurological problems, contraindications for undergoing a MRI scan and left-handedness. 25 CD patients and 25 matched healthy controls were included in the present study. All CD patients had been treated by transsphenoidal surgery, two patients (8%) additionally underwent bilateral adrenalectomy, whereas six patients (24%) had received additional radiotherapy. One patient (4%) used antidepressants. Healthy controls were pair-wise matched for gender, age, and education and recruited by advertisements in grocery stores and via Internet. Inclusion criteria for healthy controls were age between 18 and 60 years, right handedness, no current or prior drug- or alcohol abuse, no present and past history of psychiatric or neurological disorders, no use of psychotropic medication and no contraindications for MRI scanning.

The diagnosis of CD had been confirmed in all patients. ACTH dependent Cushing's syndrome had been diagnosed based on internationally agreed guidelines, with clinical manifestations and positive biochemical tests, including increased urinary excretion rates of free cortisol, decreased overnight suppression by dexamethasone (1 mg) and elevated midnight salivary cortisol values. Cure of CD had been achieved by transsphenoidal surgery and, if necessary, followed by repeated surgery and/or postoperative radiotherapy. Cure of CD was defined by normal overnight suppression of plasma cortisol levels (< 50 nmol/liter) after administration of dexamethasone (1 mg) and normal 24-h urinary excretion rates of cortisol (<220 nmol/24 h). Hydrocortisone independency was defined as a normal cortisol response to CRH or insulin tolerance test (> 500 nmol/L). Patients were followed at our department with yearly intervals, and pituitary hormone substitution was prescribed in accordance with the results of the yearly evaluation. In patients who were glucocorticoid dependent after treatment, recovery of the pituitary-adrenal axis was tested twice a year. The dose of hydrocortisone was on average 20mg/d divided into 2-3 dosages. After withdrawal of hydrocortisone replacement for 24 hours, a fasting morning blood sample was taken for

the measurement of serum cortisol concentrations. Patients with serum cortisol concentration <120 nmol/liter were considered to have ongoing glucocorticoid dependency, and hydrocortisone treatment was restarted. Patients with serum cortisol levels of 120-500nmol/liter were tested by ACTH stimulation tests (250µg). A normal response to ACTH stimulation was defined as a stimulated cortisol >550nmol/liter. When the cortisol response to ACTH was normal, patients were tested by ITT or CRH stimulation test. When cortisol responses to these tests were <550nmol/liter, hydrocortisone treatment was restarted. Evaluation of growth hormone (GH) deficiency was done by insulin-tolerance test or arginine-GHRH test only in patients under the age of 70 years and only after at least 2 years of remission. Patients with an inadequate stimulation of GH by one of these tests were treated with recombinant human GH, aiming at IGF-1 levels between 0 and +2 SD values. In addition, the twice yearly evaluation consisted of measurement of free T_4 and testosterone levels (in male patients). If results were below the lower limit of the respective reference ranges, substitution with L-thyroxin and/or testosterone was started. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was provided. Persistent cure of CD was documented by normal values of a dexamethasone (1 mg) suppression test, urinary cortisol excretion rates, and midnight salivary cortisol levels before participation in the current study.

The estimated duration of disease was determined through patients' history by looking for the earliest physical/somatic signs. Duration of remission was calculated from the date of curative transsphenoidal surgery, or in case of persistent disease, from the date of normalization of biochemical tests after postoperative radiotherapy. Patient and treatment characteristics were collected from the patient records.

Written informed consent was obtained from all participants prior to the clinical assessment and the MRI-scan session. Our institutional review board approved the study protocol.

This study was in accordance with the principles of the declaration of Helsinki.

Study design

We scheduled a single study visit of approximately two hours for MRI scanning (60 minutes) and an interview for the evaluation of the clinical data and the assessment of psychological and cognitive functioning. Scan sessions took place between 9.00 am and 12.00 am. After the examination, participants were asked to complete several self-rating questionnaires at home for the assessment of psychopathology and cognitive functioning and to return them within a week.

Assessment of psychopathology and cognitive functioning (Appendix 1)

Presence and severity of depressive symptoms were evaluated using the Montgomery-Åsberg Depression Rating Scale (MADRS) (24;25), which was the only scale that was assessed by the interviewer, and the Inventory of Depression Symptomatology (IDS) (26). Anxiety was evaluated using the Beck Anxiety Inventory (BAI) (27) and the Fear Questionnaire (FQ) (28).

Apathy and irritability were assessed using the Apathy Scale (AS) and the Irritability Scale (IS), respectively (29;30). The Cognitive Failures Questionnaire (CFQ) was used to assess failures in perception, memory, and motor function (31).

Cushing's syndrome Severity Index (CSI)

The Cushing's syndrome Severity Index (CSI) (32) was used to assess current severity of symptoms and to retrospectively estimate (clinical) severity at the time of active disease. The CSI contains eight clinical features and can be scored on a 3-point scale, ranging from 0 to 2. A higher total score on the CSI indicates greater severity, with a range of 0–16. The information necessary for completing this index was derived from clinical history and medical files. Two raters, who reached consensus on each feature in case of discrepancy, scored the CSI. For the active phase, the CSI was scored retrospectively. The current score was evaluated based on the last yearly evaluation. The total score of the active phase and the total score of the remission phase were used in the analyses.

MRI data acquisition

Images were acquired on a Philips 3T magnetic resonance imaging system (Philips Healthcare, Best, The Netherlands), (software version 3.2.1). A SENSE-32 channel head coil was used for radio frequency transmission and reception. For each subject, anatomical images were obtained using a sagittal 3-dimensional gradient-echo T_1-weighted sequence (repetition time (TR) = 9.8 ms, echo time (TE) = 4.6 ms, matrix size 256 x 256, voxel size 1,17 x 1,17 x 1,2 mm, 140 slices, scan duration 4:56 minutes) as part of a larger imaging protocol. A neuroradiologist, blinded for the clinical details of the subjects, examined all anatomical images. Apart from incidental age-related white matter hyperintensities and effects of the post-transsphenoidal surgeryin the perisellar area, no other macroscopic abnormalities were observed in the patients and controls.

Statistical analyses and data preprocessing

The first analysis comprised the voxel-based comparison of grey matter volumes in the regions of interest (ROI) (i.e. hippocampus, amygdala, ACC) and across the whole brain between patients with predominantly long-term remission of CD and their matched healthy controls. Structural data was analyzed with FSL-VBM, a voxel-based morphometry style analysis (FMRIB's Software Library) (33). First, structural images were brain-extracted and grey matter-segmented (34). The resulting grey matter partial volume images were then aligned to MNI152 (T_1 standard brain average over 152 subjects; Montreal Neurological Institute, Montreal, QC, Canada) standard space, using affine registration (35), followed by nonlinear registration. The resulting images of all participants were averaged to create a study-specific template, to which the native grey matter images were then non-linearly re-registered.

The Jacobian of the warp field obtained in this registration reflects the voxel-wise relative volume change between the original and the study specific template (i.e. a Jacobian of 5 indicates that a volume in the original image has been shrunk by a factor of 5). In order to correct for local expansion or contraction, the registered partial volume images were then modulated by dividing by the Jacobian of the warp field. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. The Gaussian outputs a weighted average of each voxel's neighborhood, with the average weighted more towards the value of the centrally located voxels. The application of this type of smoothing reduces the noise in the data substantially.

The Harvard-Oxford Cortical and Subcortical Structural Atlases implemented in FSL were used to create masks for our regions of interest: the bilateral hippocampus, the bilateral amygdala and the ACC. Probability range was set to 50-100% for all three structures. The study-specific template was then applied to this mask to create a study specific template of the grey matter values in the regions of interest only. Finally, groups were compared using a general linear model (GLM) including age, gender and level of education as confound regressors. A voxel-wise GLM was applied using permutation-based (5000 permutations) non-parametric testing, correcting for multiple comparisons across space. First, groups were compared in our regions of interest, using the created mask. Second, an exploratory whole brain VBM analysis was done, using the study-specific grey matter image as a mask to investigate whether any unpredicted differences existed between CD patients and controls. To explore possible differences between patients with hydrocortisone substitution (n=13) and patients without substitution (n=12), these two steps were repeated contrasting these two groups. Threshold-free Cluster Enhancement was used for finding clusters in the data (36), with thresholds for both the regions of interest comparison as well as the whole brain analysis set on $P<0.05$, corrected. In addition to the VBM analysis, we used FMRIB's integrated registration and segmentation tool (FIRST) to perform an automated segmentation of the amygdala and the hippocampus, allowing both shape and volume analyses.

The second analysis compared patients with predominantly long-term remission of CD and their matched healthy controls, on measures of psychological and cognitive functioning. Data from questionnaires were analyzed using SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL). All data are presented as numbers and percentages, means and standard deviations (SD) or median and interquartile range (IQR). The assumption of normal distribution was tested using the Kolmogorov-Smirnov Test and the assumption of equal variances with a Levene's Test. With respect to psychological and cognitive functioning, normally distributed continuous variables between patients and matched controls were compared using t-tests, and non-normally distributed continuous variables (MADRS, IDS, BAI, FQ, AS, CFQ) using Mann-Whitney U tests. Considering the overlap in phenomenology assessed by the questionnaires, a strict correction for multiple testing might be too conservative, therefore all tests were two-sided with $P<0.05$ uncorrected.

A third analysis was conducted in the patient group. In this analysis, we examined voxel-wise correlations of behavioural and clinical characteristics with grey matter volume in the areas resulting from the ROI analysis and the whole brain analysis. The possible influence of radiotherapy could not be properly examined, considering the small number of patients that had received radiotherapy. The level of significance was set at $P<0.05$.

RESULTS

Patient characteristics

As expected, patients and matched healthy controls did not differ in age, gender and education. The mean estimated duration of active disease was 7.9 ± 7.9 years (range 0.8 - 37.0). The mean duration of remission was 11.2 ± 8.2 years (range 0.8 - 29.4). Hydrocortisone replacement therapy was given to 13 patients (52%). The mean CSI score during active disease was 8.1 ± 2.0, and 2.5 ± 1.5 at the time of evaluation (i.e. long-term remission) (Table 1).

Table 1. Clinical characteristics of patients with predominantly long-term remission of Cushing's disease (n = 25)

	CD patients (n=25)	**Matched controls (n=25)**	**P value**
Gender (male/female)	4/21	4/21	1.000[a]
Age (years)	45 ± 8	47±7	0.471[b]
Education			0.946[a]
Low	6 (24%)	6 (24%)	
Medium	12 (48%)	11 (44%)	
High	7 (28%)	8 (32%)	
Surgery			
Transsphenoidal adenomectomy	25 (100%)		
Bilateral adrenalectomy	2 (8%)		
Radiotherapy	6 (24%)		
Disease duration (years)	7.9 ± 7.9		
Duration of remission (years)	11.2 ± 8.2		
Hypopituitarism			
Any axis	14 (56%)		
GH	10 (40%)		
LH/FSH	9 (36%)		
TSH	10 (40%)		
ADH	3 (12%)		
Hydrocortisone substitution	13 (52%)		
Hydrocortisone dose (mg/d)	20.0 (0.0 – 20.0)		
Clinical severity index			
Active phase, total	8.1 ± 2.0		
Remission phase, total	2.5 ± 1.5		

P values were tested with: [a]Chi-square test, [b]independent-sample t-test.
Data are presented as mean ± SD or number (%) or by median IQR.

MRI Analyses

Region of interest analyses

The VBM-analysis, in patients in with predominantly long-term remission of CD showed smaller grey matter volumes in a large part of the bilateral ACC in comparison with controls. Closer examination of the data revealed that the patients had an average of 14% smaller grey matter volumes in the ACC compared to matched healthy controls. There were no grey matter volume differences in the bilateral hippocampus and amygdala (Figure 1A). We observed no greater grey matter volumes in any of the ROIs in CD patients, compared to controls. Furthermore, within the patient group no differences were found in grey matter volumes between patients with hydrocortisone substitution and patients without substitution. The FIRST analysis showed similar results, with no differences in both shape and volume of the bilateral amygdala and bilateral hippocampus, between patients and controls.

Whole brain analysis

Patients with predominantly long-term remission of CD showed smaller grey matter volumes in the left perigenual region (Brodman's area between BA 32 and BA 12) of the ACC, compared to controls (Figure 1B). Greater grey matter volumes were found in the posterior lobe of the left cerebellum in CD patients compared to controls (Figure 1C). On average patients showed 34% larger grey matter volumes in the left posterior lobe of the cerebellum compared to controls ($P<0.05$). When the threshold was lowered to $P<0.10$ an additional similar effect was observed in grey matter volumes of the right posterior lobe of the cerebellum. Within the patient group, no differences were found in grey matter volumes between patients with hydrocortisone substitution and patients without substitution.

Psychopathology and cognitive functioning among patients and controls

Table 2 shows that patients with predominantly long-term remission of CD had more depressive symptoms ($P<0.005$) compared to controls, as assessed with the MADRS and the IDS. The mean total score on the MADRS was 6.3, indicating mild depressive symptoms. Furthermore, CD patients experienced more anxiety ($P=0.003$), more social phobia ($P=0.034$), and a greater degree of apathy ($P=0.002$), with 44% of patients having a score of 14 or higher, which is indicative of clinically relevant apathy. On the Irritability scale, 36 % of the patients had a score of 14 or higher, which is indicative of clinically relevant irritability. In addition, CD patients reported more cognitive failure ($P=0.023$) compared to controls. No other significant between-group differences were found. Within the patient group, no significant differences were found in psychopathology and cognitive functioning between patients with hydrocortisone substitution and patients without substitution.

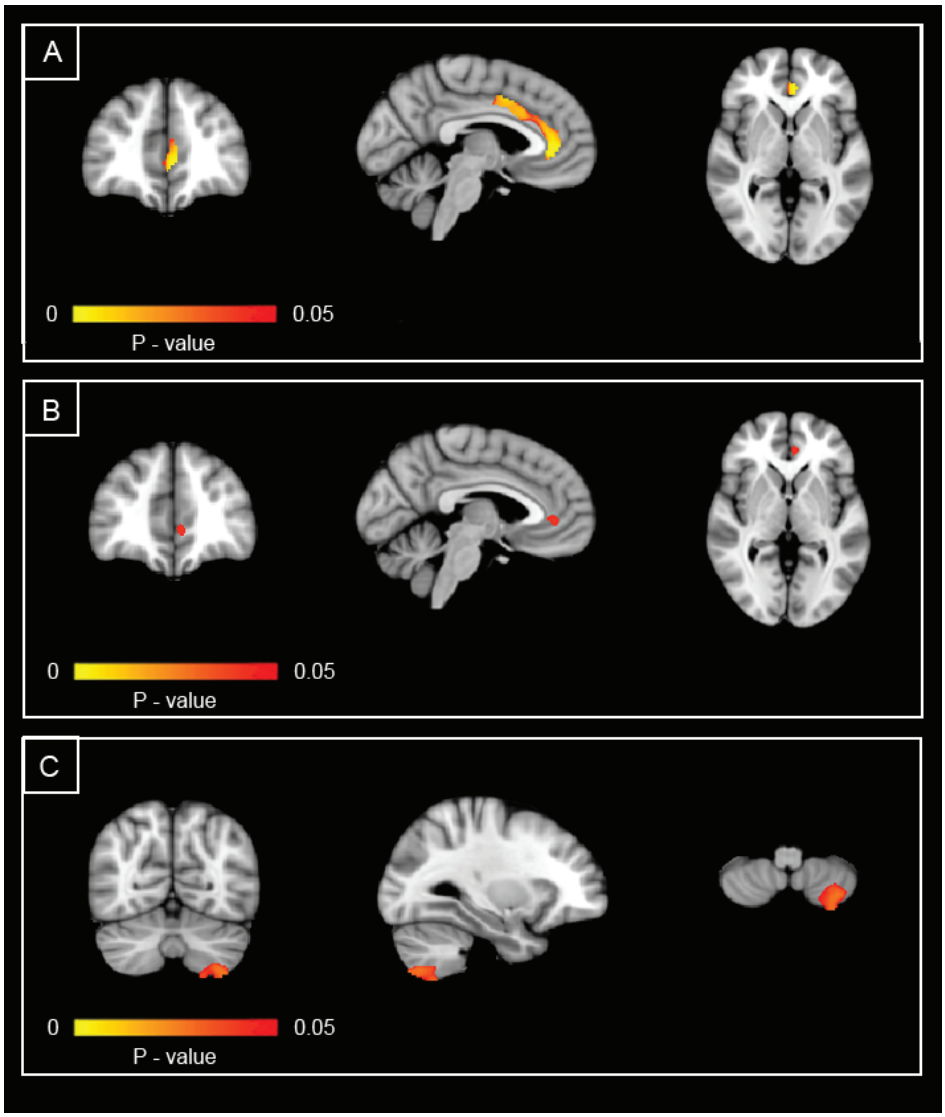

Figure 1. VBM analysis results.
A): Results of regions of interest analysis, with grey matter volumes in patients < controls (P < 0.05; 617 voxels, 2mm isotropic).
B): Results of whole brain analysis with grey matter volumes in patients < controls (P < 0.05; 37 voxels, 2mm isotropic).
C): Results of whole brain analysis with grey matter volumes in patients > controls (P < 0.05; 323 voxels, 2mm isotropic). Effects are presented on the MNI-152 1mm standard brain at a threshold of P < 0.05. Coordinates are x = -4, y = 42, z = 0 for Fig. 1a and 1b and x = -29, y = -66, z = -56 for Fig. 1C. The left hemisphere corresponds with the right side of the image.

Table 2. Psychopathology and cognitive failure questionnaires: patients with predominantly long-term remission of Cushing's disease vs. matched controls

	Cushing's disease (n = 25)	Matched controls (n = 25)	P value
MADRS	6.3 ± 5.5	1.4 ± 1.8	**0.000**[b]
Inventory depression scale (IDS)	46.8 ± 13.0	36.3 ± 5.8	**0.005**[b]
Beck Anxiety inventory (BAI)	28.4 ± 5.7	24.0 ± 3.1	**0.003**[b]
Fear Questionnaire (FQ)	24.5 ± 17.4	14.2 ± 10.0	0.051[b]
agoraphobia subscale	6.1 ± 7.9	3.4 ± 4.7	0.477[b]
blood injury phobia subscale	6.2 ± 8.3	3.2 ± 4.1	0.118[a]
social phobia subscale	12.2 ± 8.0	7.6 ± 4.9	**0.034**[b]
Irritability scale (IS)	12.1 ± 8.7	8.0 ± 6.1	0.066[a]
Total score > 14	9 (36%)	6 (24%)	
Apathy scale (AS)	13.6 ± 6.6	7.8± 3.8	**0.002**[b]
Total score > 14	11 (44%)	2 (8%)	
Cognitive failure questionnaire (CFQ)	38.0 ± 16.5	27.6 ± 9.7	**0.023**[b]

P values were tested with: [a] independent-sample t-test, [b] Mann-Whitney U test.
Level of significance was set at P<0.05 and significant values are in bold.
Data are presented as mean ± SD or number (%).

Furthermore, in the patient group no significant associations between grey matter volumes in the ACC and cerebellum, and scores on the distinguishing psychometric instruments (MADRS, IDS, BAI, AS, CFQ) were found using a voxel-wise correlation approach. Also, no significant associations between grey matter volumes of the areas of effect and clinical characteristics (i.e. estimated disease duration, duration of remission, Clinical Severity Indexes; active and remission subscale) (data not shown) were found.

DISCUSSION

The present study demonstrates that structural abnormalities in the brain are present in patients cured from CD, despite long-term remission. The data indicate that in comparison to matched healthy controls, volumes of areas in the ACC were smaller, whereas grey matter volumes of the left posterior lobe of the cerebellum were larger in patients. There were no significant differences in grey matter volumes in the hippocampus or amygdala between the two groups. These findings may support the hypothesis that the increased prevalence of depressive symptoms, anxiety, apathy and cognitive impairments observed in patients with long-term cured CD (22;23) is associated with structural brain changes. However, in these patients no significant correlations were found between psychological dysfunction and clinical characteristics on the one hand, and the grey matter volumes of the ACC and left posterior lobe of the cerebellum on the other hand.

We confirmed our hypothesis that the ACC would be affected in cured CD. The amygdala and hippocampus are connected to the anterior regions of the ACC and constitute a neural circuitry for stress reactivity and modulation (37). Dysfunction of this circuitry is implicated in mood and anxiety disorders (38). In addition, patients with stress-related psychopathology show a reduced volume of the ACC (39;40). In accordance, reduction of ACC volume is also found in animals exposed to hypercortisolism (8) and in elderly humans with dysregulation of the HPA-axis (10). Importantly, the ACC is involved in cognitive-affective processes such as assessing the projection of emotional and motivational stimuli and the regulation of emotional responses (41), and mediates ongoing behavioral adaptation (42). Therefore, the identified abnormalities of the ACC may be involved in disturbances of cognitive and emotional functioning identified in CD (43) and in patients after long-term remission of CD (4;22;23). However, in the current study we were not able to demonstrate a correlation between the observed brain changes and quantitative estimates of psychopathology. This may be due to power problems or limitations of the clinical rating scales for psychopathology. An alternative hypothesis could be that the identified structural abnormalities may also underlie or reflect abnormalities in functional or structural connectivity.

In the exploratory whole brain analysis we found an enlarged volume of the left cerebellum in patients with predominantly long-term remission of CD. When we lowered the threshold, grey matter volumes of the right cerebellum were also found to be enlarged in patients with predominantly long-term remission of CD, indicating that this effect might be bilateral. Interestingly, the cerebellum is susceptible to increased cortisol levels (44) and it is involved in motor functioning, as well as cognitive and emotional functioning (45). Intriguingly, a study by Spinelli et al. (2009), reported that individuals exposed to an extremely stressful environment developed a larger cerebellum (46). Another research group investigated the effect of chronic stress on cortical and striatal circuits (required for goal-directed behavior and habits) in rats. They found global hypertrophy of the dorsolateral striatum and atrophy of the dorsomedial striatum and suggested that the reorganization of the corticostriatal circuits after chronic stress is bidirectional, based on hypertrophy and atrophy of neuronal dendritic trees (47). This mechanism of bidirectional reorganization could also provide an explanation for the larger volume of the cerebellum in our patients treated for CD.

Contrary to our hypotheses, we did not find alterations in the hippocampus and amygdala. However, it might be that these brain structures were affected during active disease (11-13), but that grey matter volumes increased after biochemical cure. This would be in accordance with the previously found increase in hippocampal volume in CD patients after correction of hypercortisolism (11;14-16) and the well-documented plasticity of hippocampal neurons in animal models (48). Nevertheless, children experienced cognitive decline despite reversal of brain atrophy one year after surgical remission (49) and adult patients with long-term remission of CD still demonstrated impaired memory function (23). Recently, a potential mechanism was provided for this persisted memory impairment, by demonstrating that

in comparison to healthy matched controls, patients in remission of CD show biochemical abnormalities in the hippocampus, without hippocampal volume reduction (50). Studies in animals have documented that other brain areas also show structural changes in response to increased cortisol levels (47). However, the plasticity (in this case the extent of reversibility) of these non-hippocampal structures in CD is still unknown. Since there are no studies that have focused on other brain structures in patients with active CD, like the ACC or amygdala, it is not clear when these structural changes occur and how they develop over time.

For direct effects of glucocorticoids on a brain area, either the MR or GR has to be present in this area. Using data on human brain tissue arrays available from 'The Allen Institute for Brain Science', a high expression was demonstrated of both MR and/or GR, not only in the hippocampus, ACC and amygdala, but also in the cerebellum (51). Taken into account the effects found in our study, which were limited to the ACC and cerebellum, one can conclude that expression of MR and/or GR in a brain area is necessary, but not predictive of structural changes following chronic overexposure to glucocorticoids. A possible alternative explanation is that structural changes may also occur via transsynaptic mechanisms. Such mechanisms have been suggested for (transient) morphological changes in the hippocampal CA3 area, which itself expresses very low numbers of GRs, but receives input from the cortisol sensitive dentate gyrus (52).

To our knowledge, our study is the first to show that structural abnormalities in the brain are present in patients cured from CD, despite long-term remission. Strengths of our study are the homogeneity of our patient cohort with regard to treatment (i.e. all patients had been treated with transsphenoidal surgery) and the careful selection of controls. Nevertheless, heterogeneity still existed in the patient group with regard to disease duration and duration of remission, which may have decreased the power of this study. Although a sample size of 25 in both groups is appropriate for the evaluation of structural changes with MRI (53), our study might have been underpowered to detect possible correlations between clinical data, psychological and cognitive measures, and grey matter volumes within the patient group, and to detect grey matter differences between patients with or without hydrocortisone substitution. In addition, cognitive functions were assessed using a questionnaire (i.e. CFQ), and although this questionnaire has been validated repeatedly, it is no substitute for extensive neuropsychological testing, which gives a more accurate representation of cognitive functioning. Furthermore, because of our cross-sectional design it cannot be excluded that structural abnormalities were already present in patients before onset of CD. The use of a longitudinal design in future research could provide more insight into the course of the found abnormalities.

In general, alterations in grey matter volume in adults with pathology have been found to be associated with dysfunctions of specific areas or related circuitry. However, the absence of volumetric differences does not exclude functional alterations in brain areas and circuits. It should also be acknowledged that a volumetric VBM approach does not reveal the underly-

ing changes or pathology in grey matter microstructure, i.e. at the level of neurons or glia cells. Subsequently, at present there are no data available on abnormalities at the level of neurons or glia cells after chronic overexposure to glucocorticoids that may shed more light on the nature of the observed structural abnormalities. Therefore, conclusions about functional alterations in the specific brain areas cannot be drawn based solely on our findings. Exploring functional brain characteristics in our sample would be an important next step to further elucidate the neurobiological basis of psychological dysfunction in patients with remitted CD.

The data presented in this study provide a further perspective towards detailed phenotyping of patients after treatment of CD, who have always been considered cured after long-term remission of hypercortisolism. In agreement with others, CD and possibly Cushing's syndrome as well, could be a unique model to study the apparently prolonged, or even irreversible, effects of increased cortisol exposure on the brain. It is tempting to speculate that these findings, to a certain extent, could also apply to patients with chronic or recurrent forms of highly prevalent stress-related disorders, and, in addition, to patients chronically treated with exogenous corticosteroids, that are commonly prescribed to suppress the immune system (54).

In summary, the present study demonstrates that patients with long-term cure after treatment for CD have profound structural alterations in the brain, with smaller volumes of an area in the ACC and greater volumes of the left posterior lobe of the cerebellum, and report more depressive symptoms, anxiety, social phobia, apathy, and cognitive failure, compared to healthy controls. The findings suggest possible structural substrates for long-term psychological effects of hypercortisolemia in CD. Clearly, more research is needed to increase our insight in the underlying mechanisms and the trajectory of changes, which may also lead to the identification of 'critical time windows' or potential targets for prevention.

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APPENDIX 1. DESCRIPTION OF USED PSYCHOPATHOLOGY AND COGNITIVE FAILURE QUESTIONNAIRES.

Inventory of Depression Symptomatology (IDS) is a 28-item multiple-choice questionnaire, which is designed to measure severity of depressive symptoms. A higher total score indicates greater severity of depressive symptoms (24).

Montgomery-Åsberg Depression Rating Scale (MADRS) is a 10-item questionnaire which focuses on the most commonly occurring symptoms of depressive illness (i.e. apparent sadness, reported sadness, inability to feel, difficulty in concentration, inner tension, pessimistic thoughts, suicidal thoughts, lassitude, reduced sleep, reduced appetite). A higher total score indicates more severe depression (22), with severity grades: 0-6 = absent, 7-19 = mild, 20-34 = moderate, 35-60 = severe (23).

Beck Anxiety Inventory (BAI) is a 21-question inventory which evaluates anxiety. For each question the participant was asked to chose between 4 answers, ranging from 1 = not al all, to 4 = severely. A higher sum score indicates greater severity of anxiety (25).

Fear questionnaire (FQ) is a 24-item questionnaire assessing phobic anxiety. Each question can be answered on an 8-point Likert scale, ranging from 0 = would not avoid it, to 8 = always avoid it. For the present study, we only used the items necessary for the total phobia score (item 2-16). This total phobia score can be divided into three subscales: the agoraphobia subscale, the blood injury phobia subscale and the social phobia subscale. Higher scores indicate greater severity of phobias (26).

Apathy Scale (AS) consists of 14 questions on a 4-point scale. The items ranges from 0 = no apathetic behavior, to 3 = maximum intensity of apathetic behavior. A total score can range from 0 to 42 points, with higher scores indicating greater apathy. A total score of 14 points or more is being used to characterize subjects as apathetic (27;28).

Irritability Scale (IS) consists of 14 items on a 4-point scale. The items ranges from 0 = no irritable behavior, to 3 = maximum intensity of irritable behavior. Sum scores can range from 0 to 42, with higher scores indicating greater irritability. A total score of 14 point or more is being used to characterize subjects as irritable (28).

Cognitive Failures Questionnaire (CFQ) measure ones failures in perception, memory, and motor function. On this 25-item questionnaire each question can be answered on a 5-point Likert scale, ranging from 0 = never, to 4 = very often. A higher sum score indicates that an individual experiences greater cognitive failure (29).

CHAPTER 4

Altered neural processing of emotional faces in remitted Cushing's disease

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ABSTRACT

Patients with long-term remission of Cushing's disease (CD) demonstrate residual psychological complaints. At present, it is not known how previous exposure to hypercortisolism affects psychological functioning in the long-term. Earlier Magnetic Resonance Imaging (MRI) studies demonstrated abnormalities of brain structure and resting-state connectivity in patients with long-term remission of CD, but no data are available on functional alterations in the brain during the performance of emotional or cognitive tasks in these patients.

We performed a cross-sectional functional MRI study, investigating brain activation during emotion processing in patients with long-term remission of CD. Processing of emotional faces versus a non-emotional control condition was examined in 21 patients and 21 matched healthy controls. Analyses focused on activation and connectivity of two a priori determined regions of interest: the amygdala and the medial prefrontal - orbitofrontal cortex (mPFC-OFC). We also assessed psychological functioning, cognitive failure, and clinical disease severity.

Patients showed less mPFC activation during processing of emotional faces compared to controls, whereas no differences were found in amygdala activation. An exploratory psychophysiological interaction analysis demonstrated decreased functional coupling between the ventromedial PFC and posterior cingulate cortex (a region structurally connected to the PFC) in CD-patients.

The present study is the first to show alterations in brain function and task-related functional coupling in patients with long-term remission of CD relative to matched healthy controls. These alterations may, together with abnormalities in brain structure, be related to the persisting psychological morbidity in patients with CD after long-term remission.

INTRODUCTION

Cushing's disease (CD) is characterized by elevated endogenous cortisol levels and is related to physical and psychological morbidity in more than 70% of the patients (1). After correction of hypercortisolism, physical and psychological symptoms improve substantially. However, patients with long-term remission of CD still demonstrate residual physical and psychopathological morbidity (2,3), impairments in cognitive functioning (4–7) and reduced quality of life (8). A recent study provided evidence for a role of specific genetic polymorphisms in the etiology of cognitive impairments in these patients (9), but the persistent symptoms in patients with long-term remission of CD are still ill-understood. Cortisol acts in the central nervous system by stimulation of mineralocorticoid receptors and glucocorticoid receptors. An appropriate balance in activation of these two receptor systems is required for adequate stress responses. Hyperactivation of the hypothalamic-pituitary-adrenal (HPA)-axis during active CD not only induces overactivation of the receptors, but also an imbalance in mineralocorticoid- and glucocorticoid receptor activation, both of which might result in inadequate stress responses and enhanced vulnerability to psychopathology (10). The residual psychological and cognitive morbidity after long-term remission of CD suggests that exposure to hypercortisolism not only has acute effects, but might also be related to persistent changes in the brain.

Several neuroimaging studies have observed changes in morphology and function of the brain during the active phase of CD (11). Using functional Magnetic Resonance Imaging (fMRI), less activation in the left anterior superior temporal gyrus and higher activation in frontal, medial, and subcortical regions during the identification of emotional faces was measured, indicating altered activity of brain structures relevant to the perception, processing and regulation of emotion (12). In addition, adolescents with active CD demonstrated increased activation in the left amygdala and right anterior hippocampus during a memory task involving emotional faces (13). Moreover, patients with active CD showed structural brain abnormalities, including hippocampal volume reduction and cerebral atrophy (14,15). Mainly short term follow-up studies (duration of follow-up: 6-40 months) demonstrated at least partly reversibility of these structural brain abnormalities (14,16), although no firm conclusions can be drawn about the completeness of reversibility since long-term follow-up studies are lacking. Recently, we and others have shown that patients with long-term remission of CD (mean duration of remission: 11.2 years) still have abnormalities in brain structure, as evidenced by smaller grey matter volumes in the anterior cingulate cortex, larger grey matter volumes in the left lobe of the cerebellum (17) and widespread reductions in white matter integrity (18). In addition, these patients showed increased resting-state functional connectivity of the anterior cingulate cortex (19). Furthermore, a spectroscopy study by Resmini and colleagues demonstrated persistent biochemical alterations in both the left and right hippocampus in cured CD patients (20). Taken together, these findings indicate that patients with long-term remission of CD have persisting structural and biochemical brain

abnormalities, as well as changes in functional connectivity at rest, after cure of previous hypercortisolism (11). However, it is presently unknown whether these alterations appear in conjunction with altered brain activity patterns during the performance of cognitive or emotional tasks.

Given the link between hypercortisolism and disturbances in the stress response (10), and the irritability, anxiety, and depressive symptoms reported by patients with long-term remission of CD (2), we decided to examine brain activity during the processing of emotional faces in these patients. Patients were part of the sample described previously (17–19). Focus was on two regions of interest (ROIs): the amygdala and the medial prefrontal – orbitofrontal cortex (mPFC-OFC) (21). The amygdala and the mPFC, including the orbitofrontal cortex, are both part of the limbic system and involved in the regulation of the HPA-axis (22). Previous neuroimaging studies in patients with stress-related psychiatric disorders demonstrated hyperactivation of the amygdala and hypoactivation of the mPFC in response to emotional stimuli (23,24), and it has been suggested that disturbances in the amygdala – mPFC circuitry lead to symptoms of anxiety (22). Considering the similarity in psychopathology between patients with CD and patients suffering from stress-related psychiatric disorders, we hypothesized that patients with long-term remission of CD would also show hypoactivaton of the mPFC combined with hyperactivation of the amygdala, relative to matched controls.

In addition to the ROI analyses, we performed a whole-brain analysis to examine task-related activation in other brain regions. Furthermore, we investigated potential associations between brain activity and psychological and cognitive measures, and several clinical characteristics (e.g. hydrocortisone dependency and disease severity). In addition, we used psychophysiological interaction analyses (25) to explore group differences in functional connectivity during processing of emotional faces.

MATERIAL AND METHODS

Participants

Patients with long-term remission of CD of pituitary origin, monitored yearly at our institute, were invited by letter to participate in this study (n=49; age 18-60 years). Patients who did not respond to the invitation letter were contacted by phone. Thirty-one CD-patients were willing to participate and were screened for eligibility. Exclusion criteria were past or present drug- or alcohol abuse, neurological disorders, general contraindications for undergoing a magnetic resonance imaging (MRI) scan and left-handedness. Healthy control participants were recruited by advertisements in grocery stores and via Internet and were included based on the following inclusion criteria: no neurological or psychiatric disorders (past or present), no psychotropic medication, right-handedness and no contraindications for MRI-scanning. A total of 25 CD-patients and 30 controls took part in this study. Three CD-patients and

eight controls were excluded from the final analyses because of behavioral data indicating insufficient task participation (see Analysis behavioral data). Next, the remaining CD-patients and controls were matched on gender, age and education, resulting in a final sample of 21 CD-patients and 21 controls.

The diagnosis of CD had been confirmed in all patients. Criteria for diagnosis as well as for biochemical cure were applied as previously described (4). Duration of disease was estimated by looking for the earliest physical/somatic signs in the patient's history. The duration of remission was calculated from the date of curative transsphenoidal surgery, or in case of persistent disease, from the date of normalization of biochemical tests after postoperative radiotherapy. Written informed consent was obtained from all participants prior to the clinical assessment and the MRI-scan. The study protocol was approved by the medical ethical committee of the Leiden University Medical Center.

Study procedure

Each participant visited the Leiden University Medical Center for a two-hour session consisting of an interview for the evaluation of clinical data, assessment of psychopathology and cognitive functioning, and an MRI-scan. At the end of the session, participants were asked to complete several self-rating questionnaires at home for the assessment of psychopathology and cognitive functioning and to return them within a week. One CD-patient did not return the questionnaires.

Assessment of psychopathology and cognitive functioning

The assessment of psychopathology and cognitive functioning took place as described earlier (17,18). Presence and severity of depressive symptoms was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS; (26)) and the Inventory of Depression Symptomatology (IDS; (27)). Anxiety was evaluated using the Beck Anxiety Inventory (BAI; (28)) and the Fear Questionnaire (FQ; (29)). Apathy and irritability were assessed using the Apathy Scale (AS; (30)) and the Irritability Scale (IS; (31)). Failures in perception, memory, and motor function were evaluated using the Cognitive Failures Questionnaire (CFQ; (32)).

Cushing's syndrome Severity Index (CSI)

The Cushing's syndrome Severity Index (CSI; (33)) was used to evaluate current severity of symptoms and to retrospectively estimate clinical severity at the time of active disease. A higher total score on the CSI indicates greater disease severity. The information necessary for completing this index was derived from clinical history and medical files. Two raters, who reached consensus on each feature in case of discrepancy, scored the CSI.

The Faces task

The fMRI Faces task was based on the event-related emotional faces paradigm reported by (34); the task described here has been employed earlier (35,36). The task presents 120 color photographs of faces with angry, fearful, happy, neutral and sad expressions (task-condition) and 80 scrambled faces (control-condition). Photographs were selected from the Karolinska Directed Emotional Faces System (37) and represented standardized facial expressions of emotions expressed by amateur actors. For each facial expression, 24 photographs were selected (12 male faces, 12 female faces). Duration of stimulus presentation (both of faces and scrambled faces) was 2.5 s. Between stimuli, a black screen was presented with a random duration between 0.5 and 1.5 s. An event-related design was used to reduce anticipatory effects. During the task-condition, participants were instructed to indicate the gender of the presented face by pressing buttons of magnet-compatible button boxes attached to their legs. During the control-condition, participants were instructed to press the button corresponding to the direction of an arrow presented over the scrambled face. Reaction time and accuracy were recorded. The task was presented using E-prime software (Psychology Software Tools, Pittsburgh, PA). Images were projected onto a translucent screen, which was visible for participants by means of a mirror above their head. Average duration of the task was 11.8 minutes.

Analysis behavioral data

Behavioral data of the Faces task were processed using custom-written scripts in Matlab (Mathworks). Data were filtered for each participant by removing trials with reaction times ≤ 300 ms and trials with reaction times more than three standard deviations apart from the mean individual reaction time, following the procedure described by (38). This filtering procedure was applied to remove extreme outlier trials from the subsequent analysis of performance, and eliminated on average 13.21% of trials (CD-patients: 13.24%; controls: 13.18%; no difference between groups (independent-samples t-test: $t(53)=0.06$, $P=0.94$)). Participants with a percentage of missing trials exceeding the upper bound of the 95% confidence interval for the mean percentage of missing trials for each group were excluded. This was the case for two CD-patients and three controls. Subsequently, performance (accuracy and reaction time) was determined for each participant, for all trials and for particular task conditions (scrambled faces; facial expressions; separate for the five different facial expressions: angry, fearful, happy, neutral and sad). Participants with an overall accuracy ≤ 80% (one CD-patient; five controls) were excluded from the dataset. After matching on age, gender and education, 21 CD-patients and 21 controls formed the final sample of this study.

Statistical analyses of performance were performed using IBM SPSS Statistics for Windows (Version 21.0. Armonk, NY: IBM Corp). Repeated measures ANOVAs with condition (facial expressions vs scrambled faces) as within-subjects factor and group (CD-patients vs controls) as between-subjects factor were used to investigate group differences in performance (ac-

curacy and reaction time). In addition, repeated measures ANOVAs with facial expression (angry, fearful, happy, neutral, sad) as within-subjects factor and group (CD-patients vs controls) as between-subjects factor were used to examine whether facial expression influenced performance of the groups. Significance level was set at $P \leq 0.05$.

MRI data acquisition

Imaging data were collected using a Philips 3.0T Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands), equipped with a 32-channel SENSE (Sensitivity Encoding) head coil and located at the Leiden University Medical Centre. During the Faces task, functional scans were acquired using T2* weighted echo-planar imaging (repetition time (TR)=2200 ms, echo time (TE)=30 ms, 38 axial slices, descending acquisition, 2.75 mm x 2.75 mm x 2.75 mm + 10% interslice gap, field of view 220 x 115 x 220 mm). The first two volumes of the scan were dummy scans and were removed to allow for equilibration of T1 saturation effects. A 3D T1-weighted anatomical scan and a high-resolution EPI-image were acquired for within-subject registration purposes (T1 scan: TR=9.734 ms, TE=4.59 ms, flip angle = 8°, 140 slices, 0.875 x 0.875 x 1.2 mm, FOV = 224 x 168 x 177.333 mm; EPI high-resolution scan: TR = 2200 ms, TE = 30 ms, flip angle = 80°, 84 axial slices, 1.964 x 1.964 x 2 mm). The task was part of a larger scanning session (17-19).

fMRI data analysis

Data analysis was performed using FEAT (FMRI Expert Analysis Tool; version 6.00) (39,40). Pre-statistics processing consisted of motion correction, slice-timing correction using Fourier-space time-series phase-shifting, non-brain removal, spatial smoothing using a Gaussian kernel of FWHM 6.0 mm, grand-mean intensity normalization of the entire 4D dataset by a single scaling factor in order to enable higher-level analyses, and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with σ=30.0 s). Functional scans of each participant were registered to the individual high-resolution EPI-image, which was in turn registered to the individual 3D T1-weighted anatomical scan and subsequently registered to the Montreal Neurological Institute (MNI) T1-template brain (resolution 2 mm). Next, event-related statistical analysis of the time-series was carried out in native space. For each participant, six explanatory variables with their temporal derivatives were included in the general linear model, representing the presentation of 1) a scrambled face, 2) an angry face, 3) a fearful face, 4) a happy face, 5) a neutral face and 6) a sad face. Each EV had a duration of 2.5 s and was convolved with a double gamma haemodynamic response function. Subsequently, six contrasts of interest were defined: 1) all emotional faces > scrambled faces (referred to as "viewing faces", representing main effect of task); 2) angry faces > scrambled faces; 3) fearful faces > scrambled faces; 4) happy faces > scrambled faces; 5) neutral faces > scrambled faces and 6) sad faces > scrambled faces. We verified whether the individual scans were registered correctly and confirmed that relative motion parameters did not exceed 2.5

mm. Subsequently, the individual contrast images were submitted to higher-level mixed-effects group analyses.

Whole-brain analysis: main effect of task

A whole-brain analysis was performed to determine activity related to the main effect of task (emotional faces > scrambled faces). Clusters were tested for significance using a height threshold of z>2.3 and a cluster-corrected significance threshold of P<0.05 (41).

Region Of Interest (ROI) analyses: differences between groups

Given our a priori hypotheses about the amygdala and mPFC, we applied a ROI approach in order to maximize statistical power to detect differences in brain activation between the CD-patients and controls in these areas. To that aim, we performed two separate higher-level analyses, restricted respectively to the amygdala and the mPFC-OFC by applying pre-threshold masking. Masks were created in standard space with a resolution of 2x2x2 mm. The amygdala ROI was defined using the Harvard-Oxford Subcortical Structural Atlas implemented in FSLView (version 3.2.0) and consisted of voxels with a probability of at least 50% of belonging to the left or right amygdala (total size of mask: 505 voxels). The mPFC-OFC ROI was created using the Harvard-Oxford Cortical Structural Atlas implemented in FSLView (version 3.2.0) and consisted of voxels with a probability of at least 10% of belonging to the subcallosal cortex, the frontal medial cortex or the frontal orbital cortex. In addition, we included those voxels of the anterior division of the cingulate gyrus (probability threshold: 10%) positioned anterior of the y-coordinate of 30 mm (total size of mask: 10738 voxels). Masks are shown in Figure 1.

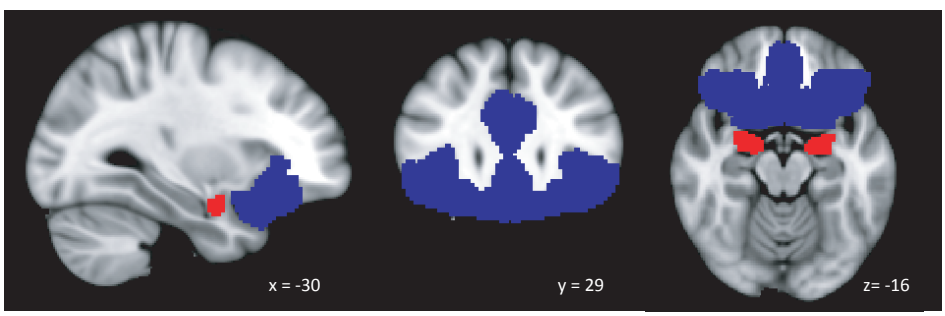

Figure 1. Regions of interest: medial prefrontal – orbitofrontal cortex (mPFC-OFC) (blue; 10738 voxels) and amygdala (red; 505 voxels), superimposed on the template MNI_T1_152_1mm_brain. All images are displayed according to radiological convention: right in image is left in brain.

Within these masks, we investigated activation related to the main effect of task (emotional faces > scrambled faces) for each group separately, and report regions with a height threshold of z>2.3 and a cluster-corrected significance threshold of P<0.05 (41). Subsequently, we

investigated group-differences related to the main effect of task. Significant group-differences within the ROIs were further explored by extracting individual mean z-scores from the lower-level contrast images of the contrast 'emotional faces > scrambled faces' with the Featquery-tool (implemented in FSL 5.0.4). Correlation analyses on these individual z-scores were performed using Pearson's r or, when data violated assumptions for parametric tests, with Kendall's tau. In addition, individual mean z-scores for the other contrasts (each facial expression > scrambled faces) were extracted from significant clusters.

Whole-brain analysis: differences between groups

In addition to the ROI analyses, we performed an exploratory whole-brain analysis to investigate task-related group-differences in brain activation outside the predefined ROIs. Clusters were tested for significance using a height threshold of $z>2.3$ and a cluster-corrected significance threshold of $P<0.05$ (41).

Post-hoc exploratory psychophysiological interaction (PPI) analyses

In order to investigate whether group-differences in activation were accompanied by differences in functional connectivity specific to the task, we performed exploratory psychophysiological interaction (PPI) analyses for significant clusters resulting from our ROI analyses. A PPI analysis investigates whether a task-condition (psychological component) influences the co-variation in activity (physiological component) between a certain seed region and other brain regions (25). For each individual, a first-level PPI analysis was performed using FEAT. Individual timecourses (physiological component) were extracted from a seed region based on the significant cluster obtained in the ROI-analyses. The psychological regressor denoted the task-condition of interest (emotional faces > scrambled faces). We convolved this regressor with a double gamma haemodynamic response function, applied temporal filtering and added a temporal derivative. The product of the demeaned physiological regressor and the zero-centered psychological regressor represented the PPI regressor of interest. In addition, a confound regressor (faces + scrambled faces) was included in the model, to explain shared variance between trial types (regressor convolved with a double gamma haemodynamic response function, temporal filtering applied and a temporal derivative added). Higher-level PPI analyses were used to test for differences between groups in task-related functional connectivity. In order to avoid false-positive results in this exploratory analysis, clusters were tested for significance using a rather stringent height threshold of $z>3.1$ and a cluster-corrected significance threshold of $P<0.05$ (41). Significant clusters were further investigated by extracting the individual z-scores using the Featquery-tool.

RESULTS

Participants

Characteristics of CD-patients and matched healthy controls are presented in Table 1. Patients had a mean estimated duration of disease of 8.2 years (standard deviation (SD): 8.5; range 0.8 – 37.0 y), while the mean duration of remission at the time of evaluation was 10.8 years (SD: 7.9; range 1.9 – 10.8 y). CSI scores during active disease and at the time of evaluation were 8.3 (SD: 2.0, range 5.0-12.0) and 2.5 (SD: 1.6, range 0.0 – 5.0), respectively. Eleven patients (52%) received hydrocortisone replacement. CD-patients had more depressive symptoms than controls on the MADRS ($P<0.001$). Scores on the other questionnaires were not different between groups when correcting for multiple comparisons (Bonferroni-corrected significance level: $P<0.005$; Table 1). However, when a less conservative threshold ($P<0.05$) was applied, patients appeared to have more depressive symptoms as measured with the IDS self-report questionnaire ($P=0.017$) and higher anxiety levels as assessed by both the BAI ($P=0.008$) and the FQ ($P=0.007$). Specifically, patients reported increased levels of social anxiety ($P=0.006$), while scores on agoraphobia and blood-injury phobia did not differ between groups. In addition, patients had higher scores on the Apathy Scale ($P=0.006$) and mentioned higher levels of cognitive failure ($P=0.023$) (Table 1). Patients with and without hydrocortisone replacement did not differ on any of these scores (data not shown).

Behavioral data

Performance scores (accuracy and reaction time) on the Faces task are presented in Figure 2 (see for detailed scores Supplementary Table 1). There were no group-differences with respect to the percentage of missing trials (i.e. trials in which no response was given; independent-samples t-test: $t(40)=-1.06$, $P=0.29$). Repeated Measures ANOVAs (condition (facial expressions vs scrambled faces) x group) revealed a significant effect of condition on both accuracy ($F(1,40)=4.09$, $P=0.05$) and reaction time ($F(1,40)=9.89$, $P=0.003$). However, there was no effect of group on performance (accuracy: $F(1,40)=0.01$, $P=0.91$; reaction time: $F(1,40)=0.13$, $P=0.72$) nor an interaction between group and condition (accuracy: $F(1,40)=0.20$, $P=0.66$; reaction time: $F(1,40) = 3.02$, $P=0.09$). Post-hoc paired-sample t-tests revealed that all participants reacted slower ($t(41)=3.1$, $P=0.004$), but were more accurate ($t(41)=-2.0$, $P=0.047$) in trials with facial expressions compared to trials with scrambled faces.

Additional repeated measures ANOVAs investigating the effect of facial expression on performance (facial expression x group) revealed no significant effect of facial expression on either accuracy ($F(4,160)=1.64$, $P=0.17$) or reaction time ($F(4,160)=1.17$, $P=0.33$). In addition, there was no significant effect of group (accuracy: $F(1,40)=2.84$, $P=0.10$; reaction time: $F(1,40)=1.30$, $P=0.26$) nor a significant interaction between facial expression and group (accuracy: $F(4,160)=0.58$, $P= 0.68$; reaction time: $F(4,160)=0.17$, $P=0.95$) (Figure 2).

Table 1 Characteristics of participants and results of psychopathology and cognitive performance. Data are presented as mean ± standard deviation or as numbers

	CD-patients (n =21)	Healthy controls (n=21)	P value
Age (years)	45.0 ± 7.9	45.9 ± 6.7	0.693 [a]
Gender (male/female)	4 / 17	4 / 17	1.000 [b]
Education (n)			
Low	5	5	1.000 [b]
Medium	10	10	1.000 [b]
High	6	6	1.000 [b]
Surgery (n)			
Transsphenoidal adenomectomy	21 (100%)		
Bilateral adrenalectomy	1 (5%)		
Radiotherapy (n)	5 (24 %)		
Disease duration (years)	8.2 ± 8.5		
Duration of remission (years)	10.8 ± 7.9		
Clinical severity index (total score)			
Active phase	8.3 ± 2.0		
Remission phase	2.5 ± 1.6		
Hydrocortisone substitution (n) Mean dose: 18.4 mg/day (± 10.3 mg)	11 (52 %)		
Montgomery-Åsberg Depression Rating Scale (MADRS)	5.9 ± 5.7	1.3 ± 1.5	0.000 [c] **
Inventory of Depression Symptomatology (IDS) #	46.2 ± 13.8	34.9 ± 3.3	0.017 [c] *
Beck Anxiety Inventory (BAI) #	28.2 ± 6.1	23.6 ± 2.8	0.008 [c] *
Fear Questionnaire (FQ) #			
Total Score	26.8 ± 17.5	13.6 ± 10.5	0.007 [a] *
Agoraphobia Subscale	6.8 ± 8.4	2.9 ± 4.9	0.242 [c]
Blood Injury Phobia Subscale	6.8 ± 8.9	3.5 ± 4.4	0.327 [c]
Social Phobia Subscale	13.2 ± 7.8	7.2 ± 5.1	0.006 [a] *
Apathy Scale (AS) #	13.2 ± 6.7	8.2 ± 3.8	0.006 [a] *
Irritability Scale (IS) #	11.7 ± 9.5	7.3 ± 4.8	0.147 [c]
Cognitive Failures Questionnaire (CFQ) #	37.9 ± 17.8	25.4 ± 8.0	0.023 [c] *

Differences between groups were tested with an independent-samples t–test ([a]), χ^2 –test ([b]) or Mann-Whitney U test ([c]).

[#]: Scores based on data from 20 CD patients.

*: Group-difference at uncorrected significance level P <0.05.

**: Group-difference at Bonferroni-corrected significance level P < 0.005.

Whole-brain analysis: main effect of task

The whole-brain analysis revealed task-related (emotional faces > scrambled faces) activation clusters in line with those reported in earlier work (34–36). In both patients and controls, significant brain activation was present in the bilateral occipital cortex and fusiform gyrus, bilateral amygdala and hippocampus, and several prefrontal areas (Figure 3A and 3B; Supplementary Table 2).

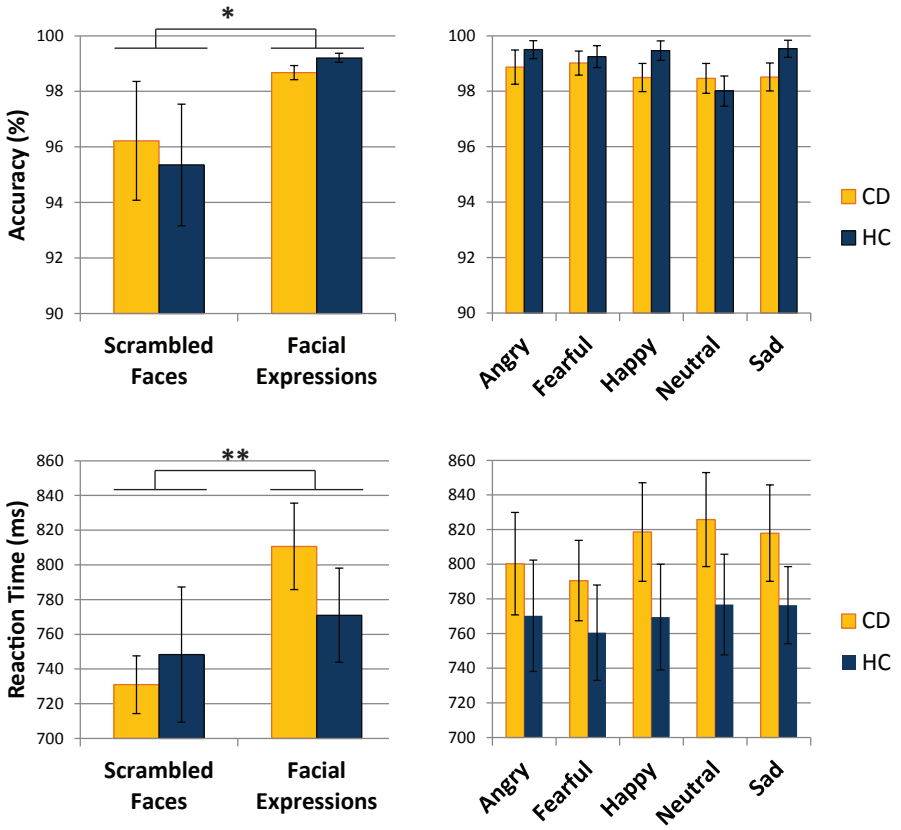

Figure 2. Performance on Faces task. Error bars represent standard error of the mean. *: P<0.05, **: P<0.005.

Region Of Interest (ROI) analyses: differences between groups

Amygdala

In line with our hypothesis and the results of the whole-brain analysis, viewing faces was associated with significant bilateral amygdala activation, both in patients with CD and controls (Supplementary Figure 1; Supplementary Table 3). There was, however, no significant difference in brain activation levels between groups at the predefined threshold (z>2.3, cluster-corrected significance threshold of P<0.05). Also when we applied a more liberal voxel threshold of P<0.01 (uncorrected), no significant activation differences between groups emerged.

mPFC-OFC

Within the predefined mPFC-OFC ROI, viewing faces was associated with activation in bilateral orbitofrontal cortex in both groups (Supplementary Figure 2; Supplementary Table 4).

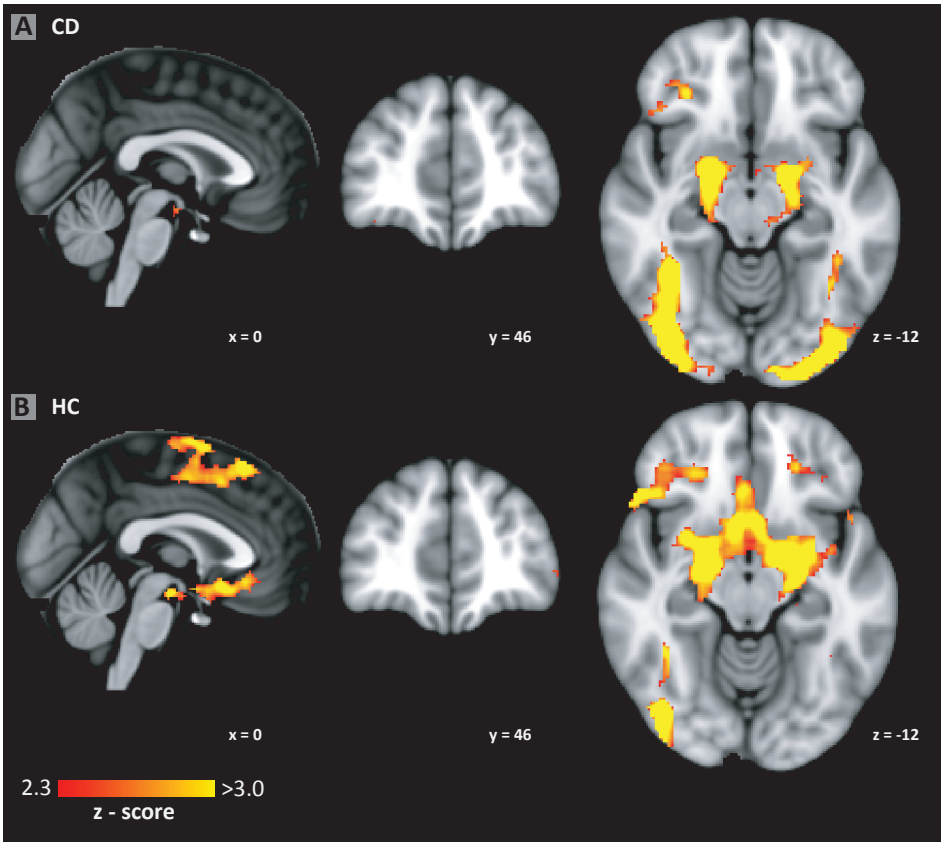

Figure 3. Significant activation clusters related to viewing faces (emotional faces > scrambled faces) at whole-brain level in CD-patients with long-term remission (CD; Figure 3A) and control participans (HC; Figure 3B). Significant clusters are superimposed on the template MNI_T1_152_1mm_brain. All images are displayed according to radiological convention: right in image is left in brain.

Group-comparisons showed decreased activation of the ventromedial PFC (vmPFC) in CD-patients relative to controls (clustersize: 274 voxels, P=0.021; Figure 4A and Supplementary Table 4). To further illustrate the group-difference in brain activation within the vmPFC, mean z-scores were extracted from the lower-level contrast images for each individual, using a mask including those voxels showing a significant group-difference (z>2.3) within the vmPFC ROI (from now on referred to as 'vmPFC group-difference mask'). Results are presented in Figure 4B.

In addition, the vmPFC group-difference mask was used to extract individual mean z-scores for the five lower-level contrasts representing activation related to the separate facial expressions (angry, fearful, happy, neutral, sad) relative to scrambled faces, in order to investigate whether the difference in vmPFC activation between the groups was influenced by specific facial expressions. A repeated measures ANOVA (facial expression x group) con-

firmed the effect of group (F(1,40)=8.65, P=0.005), but revealed no effect of facial expression (F(4,160)=1.61, P=0.19); in addition, there was no interaction between facial expression and group (F(4,160)=0.57, P=0.65) (Figure 4C). These findings indicate that the vmPFC-hypoactivation in CD-patients is not driven by viewing a face with a specific emotional expression, but rather represents an overall effect of viewing faces.

Relation between vmPFC activation and clinical characteristics

Within the group of patients, there was no relation between activation (contrast emotional faces > scrambled faces) in the vmPFC cluster and scores on the MADRS (Kendall's tau=0.22,

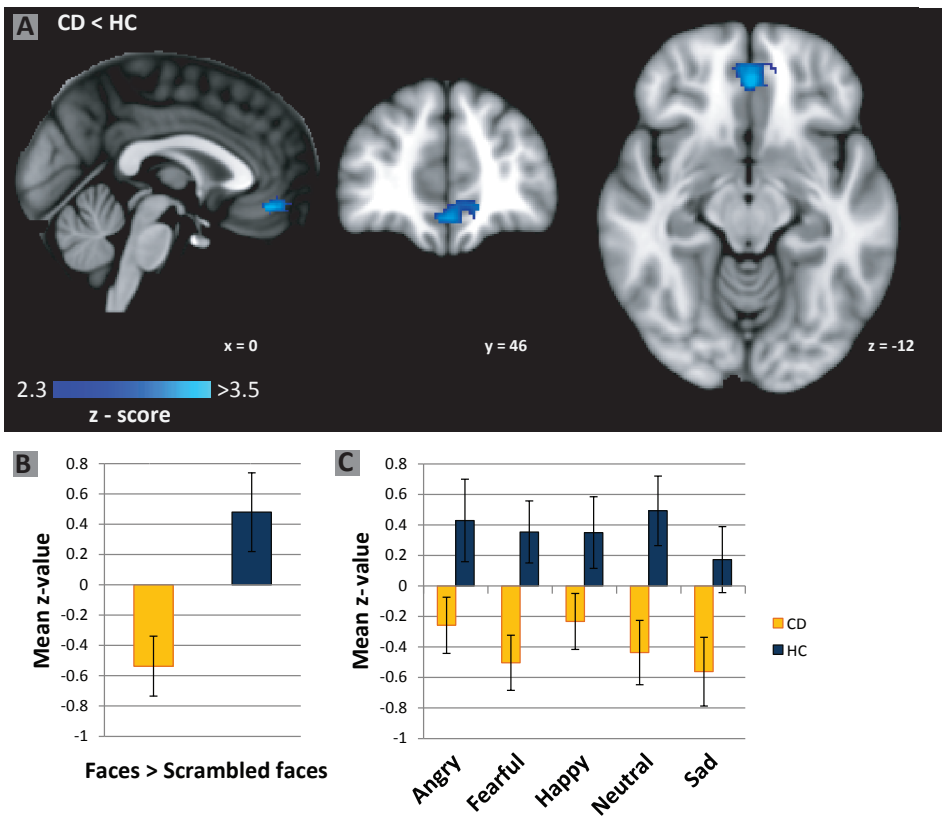

Figure 4. Significant group difference in activation related to viewing faces (emotional faces > scrambled faces) within the mPFC-OFC ROI (Figure 4A). CD-patients with long-term remission (CD) had significantly lower activation levels in the vmPFC when compared to control participants (HC). Significant clusters are superimposed on the template MNI_T1_152_1mm_brain. All images are displayed according to radiological convention: right in image is left in brain. Blue colors indicate decreased activation levels in CD-patients relative to control participants. For illustrative purposes, individual z-scores were extracted from the vmPFC cluster and presented in Figure 4B (emotional faces > scrambled faces) and Figure 4C (separate facial expressions). Analyses confirmed significantly decreased activation levels in CD-patients with long-term remission compared to controls, but no effect of facial expression.

P=0.18). In addition, there was no difference in vmPFC activation levels between patients who received radiotherapy (n=5) and patients who did not receive radiotherapy (n=16; t(19) =-0.38, P=0.71), neither was there a difference between patients with hydrocortisone replacement (n=11) and those who were not glucocorticoid dependent (n=10; t(19)=-1.5, P=0.15). Furthermore, there was no relation between vmPFC activation and disease duration (Kendall's tau=0.13, P=0.40) or the severity of symptoms as measured with the CSI during active disease (Pearson's r=-0.03, P=0.89) or during remission (Kendall's tau = 0.15, P=0.37). The relation between the duration of remission and vmPFC activation was significant at trend level (Pearson's r =-0.41, P= 0.06), indicating that a longer duration of remission is associated with more activation in the vmPFC.

Whole-brain analysis: differences between groups

Comparison of whole-brain activation levels (contrast emotional faces > scrambled faces) between the groups revealed decreased brain activation in CD-patients relative to controls in a cluster in the mPFC (Supplementary Table 2). This cluster extended into the left frontal pole (clustersize: 578 voxels, P=0.021). There were no clusters where CD-patients showed increased activation relative to controls.

Post-hoc exploratory PPI analyses

We performed a post-hoc exploratory PPI analysis with the hypoactive cluster in the vmPFC as seed region. Using the vmPFC group-difference mask, we extracted for each participant the mean time course from this region. This time course constituted the physiological regressor in the model, while the psychological regressor denoted the task-condition of interest (emotional faces > scrambled faces). Comparison of the groups revealed no significant clusters within the amygdala ROI, indicating that groups did not differ in task-related func-

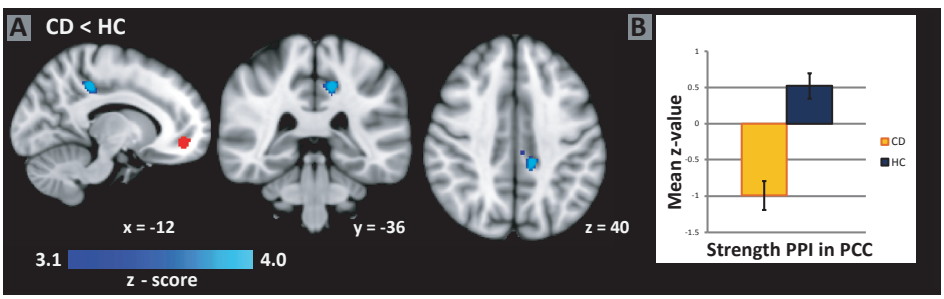

Figure 5. Significant group difference in functional connectivity during the faces vs scrambled task condition (PPI) between the vmPFC (red) and the posterior cingulate cortex (PCC; blue colors indicate decreased functional connectivity in CD- patients relative to control participants) (Figure 5A). CD-patients with long-term remission had significantly decreased positive functional coupling when compared to control participants (HC). For illustrative purposes, individual z-scores were extracted from the PCC cluster and presented in Figure 5B. Significant clusters superimposed on the template MNI_T1_152_1mm_brain. All images are displayed according to radiological convention: right in image is left in brain.

tional connectivity between the vmPFC cluster and the amygdala. Exploratory analyses at the whole-brain level revealed a significant group difference in task-condition associated changes in connectivity at the whole brain level (Figure 5): CD-patients showed a decreased positive functional coupling related to the task (emotional faces > scrambled faces) between the vmPFC cluster and the posterior cingulate cortex (PCC) relative to controls (cluster size: 139 voxels, P=0.049; maximum z-value 4.19 at MNI coordinate (X,Y,Z) -12, -34, 42).

DISCUSSION

The present study is the first to demonstrate task-related functional brain abnormalities in patients with long-term remission of CD relative to matched healthy control participants. We found hypoactivation of the ventromedial prefrontal cortex (vmPFC) during processing of facial expressions (versus scrambled faces), without alterations in amygdala activation. This vmPFC hypoactivation was not elicited by a specific facial expression. The post-hoc exploratory psychophysiological interaction (PPI) analysis, investigating task-related correlations in brain activity between regions, revealed decreased functional coupling between the vmPFC and the posterior cingulate cortex (PCC). These functional brain abnormalities may, at least in part, underlie the long-term psychological morbidity as is observed after successful correction of hypercortisolism (4).

The vmPFC hypoactivation reported here (Figure 3 and Figure 4) is in line with the results of earlier work on prefrontal functioning during emotional processing in stress-related disorders. The vmPFC is functionally and structurally connected to the amygdala and is, due to its role in fear learning and fear extinction, implicated in the pathogenesis of anxiety and mood disorders (22). Decreased mPFC activation has been reported during emotional tasks in patients with specific phobia and panic disorder (42), women with generalized anxiety disorder (43), men with posttraumatic stress disorder (PTSD) (24) and individuals reporting emotional maltreatment during their childhood (44). However, the present results are in striking contrast with earlier findings in patients with active CD, since patients with active disease demonstrated higher activation levels in frontal, medial, and subcortical regions during the identification of emotional faces (12). It should, however, be noted that this hyperactivation was accompanied by lower accuracy in task performance in patients compared to controls (12), while we did not find any group differences in task performance in our study (Figure 2; Supplementary Table 1). These findings tentatively suggest that correction of hypercortisolism may induce a switch in vmPFC activation levels from hyperactivation to hypoactivation in response to emotional stimuli. Future longitudinal research is needed to study the time course of dynamic changes that occur after correction of hypercortisolism.

We speculate that the hypoactivation in the vmPFC, in combination with the earlier described alterations in brain structure and white matter integrity in the same sample of patients (17,18), underlies the persisting psychopathology previously reported in patients with

long-term remission of CD (2,7). In line with these results, the patient sample investigated here showed an increased prevalence of depressive symptoms, anxiety levels and symptoms of apathy (Table 1). Although patients had clear symptoms and differed significantly from controls, it should be noted that their scores on depression scales were still within the normal range (26), indicating that the patients would not have been classified as having a clinical depression. This observation suggests that the functional brain changes in patients with long-term remission of CD reported here are not the result of suffering from a depressive disorder. Alternatively, this null-effect could be caused by insufficient power due to the relatively small sample size or reflect the limited sensitivity of questionnaires to measure specific elements of psychopathology. Furthermore, it is possible that the hypoactivation of the vmPFC only enhances the sensitivity to develop psychopathology, but that the actual expression of psychopathology is also dependent on other factors, such as environmental factors and personality traits. Future studies with a larger sample size could provide more insight into this relationship, as well as into the influence of other factors such as duration of remission or glucocorticoid dependency. These factors showed weak and insignificant relationships with vmPFC activation in our study, but are potentially confounding factors that should be taken into account.

As expected, we observed robust amygdala activation in response to facial expressions (Supplementary Figure 1). Contrary to our hypothesis, we did not find any group differences in amygdala activation. We expected amygdala hyperactivation in this sample of patients compared to healthy controls, based on studies reporting increased amygdala activation in patients with other stress-related disorders, such as PTSD (45), social anxiety disorder (SAD) (46), and participants with previous childhood maltreatment (35); for a review see (21). However, our results coincide with those from other studies reporting no difference in amygdala activation levels between patients and healthy controls, for example in women with generalized anxiety disorder (43), patients with generalized SAD (47) and patients with depression and anxiety (36). The absence of alterations in amygdala activity might also relate to the specifics of our task-paradigm, since the results of various experiments, reviewed by (22), suggest that task-related factors like the amount of attention and the level of awareness of the stimuli could possibly influence the level of amygdala activation in anxiety. However, more research is needed to explore this relationship between task specifics and amygdala activation levels into more detail. Alternatively, the lack of detection of a group difference in amygdala activation could possibly be caused by differences in baseline amygdala blood flow and blood oxygenation level-dependent (BOLD) responses between patients and controls, which could not be measured with the methods used in this study.

Additional post-hoc PPI analyses revealed decreased functional coupling in patients between the vmPFC and the posterior cingulate cortex (PCC) during the task-condition (emotional faces > scrambled faces) (Figure 5). The PCC is suggested to play an important role in directing attention, regulating cognition, memory-related processes and self-referential

tasks, but it's exact function is still a matter of debate (48). The mPFC and PCC are structurally connected by the cingulum tract and are functionally connected as part of the so-called default mode network (DMN) (49,50). Earlier research by our group showed decreased white matter integrity in the cingulum tract in the same group of CD patients (18). Here, we expand this finding by showing decreased functional coupling between the areas that are structurally connected by the cingulum tract. To the best of our knowledge, we are the first to report on changes in task-condition associated functional connectivity in patients with CD after long-term remission. Although this finding is preliminary due to the exploratory nature of the analysis, it is in line with the results of earlier work on stress-related disorders. For example, a recent review reported decreased functioning of the DMN in patients with anxiety disorders in tasks in which they were supposed to regulate their emotions without explicit instructions (51). In addition, Bluhm and colleagues showed decreased connectivity between the mPFC and the PCC in women with PTSD (52). However, these studies determined functional connectivity during rest, while we observed changes in task-condition dependent functional connectivity. Future research is needed to elaborate on the aberrant functional coupling between the vmPFC and the PCC in patients with long-term remission of CD, in order to investigate the direction of these changes.

The findings of this study provide new insight into the functional brain alterations underlying the persisting psychological morbidity seen in patients after treatment of CD, who have always been considered cured after correction of cortisol excess. Although no formal conclusions can be drawn about causal relations between the effects of previous exposure to excessive cortisol levels and functional brain alterations given the cross-sectional design of this study, the results presented here strongly suggest that hypercortisolism induces persistent changes in brain activation. The use of a longitudinal design in future research enables to provide more insight into the course of the described functional abnormalities.

In conclusion, the present study clearly shows long-term changes in brain activation patterns in patients with CD despite long-term remission of cortisol excess. Thereby, we have provided insight in the effects of past hypercortisolism on the brain. These functional alterations may, together with the previously reported structural abnormalities in cerebral grey and white matter, underlie the long-term psychological morbidity in patients with CD after correction of hypercortisolism. Prospective studies with a long-term follow-up could provide more insight into the longitudinal changes that occur after correction of cortisol excess.

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Supplementary Table 1. Performance on Faces Task

	CD-patients (n =21)	Healthy controls (n=21)	P-value [a]
Missings (%)	3 ± 2	3 ± 2	0.29
Accuracy (%)			
Scrambled faces	96 ± 10	95 ± 10.0	0.78
Facial expressions	99 ± 1	99 ± 1	0.09
Angry	99 ± 3	100 ± 2	
Fearful	99 ± 2	99 ± 2	
Happy	99 ± 2	100 ± 2	
Neutral	98 ± 3	98 ± 3	
Sad	99 ± 2	100 ± 1	
Reaction time (ms)			
Scrambled faces	726 ± 76	742 ± 178	0.71
Facial expressions	807 ± 114	766. ± 124	0.27
Angry	798 ± 135	764 ± 147	
Fearful	793 ± 106	755 ± 126	
Happy	814 ± 130	763 ± 140	
Neutral	817 ± 125	772 ± 133	
Sad	814 ± 127	772 ± 102	

All presented scores are mean ± standard deviation. Differences between groups were tested with an independent-samples t-test ([a]).

Supplementary Table 2. Activation clusters (whole-brain) in response to emotional faces (vs scrambled faces)

		MNI coordinates peak voxel					
	Region	**X**	**Y**	**Z**	**Max. Z value**	**# voxels**	**P-value**
HC	Bilateral amygdala and hippocampus	20	-4	-16	5.41	6729	<0.001
	Right IFG, extending into right MFG	52	22	22	4.67	4118	<0.001
	Bilateral SFG	8	14	52	4.45	1814	<0.001
	Right Temporal Occipital Fusiform Cortex, extending into LOC	38	-50	-22	6.17	1023	<0.001
	Left Temporal Fusiform Cortex, extending into ITG	-38	-42	-26	5.39	623	0.014
	Postcentral Gyrus	56	-12	46	3.38	495	0.045
CD	Right MFG, extending into right IFG	54	26	30	4.7	2880	<0.001
	Bilateral amygdala and hippocampus	20	-4	-16	5.25	2699	<0.001
	Right Occipital Fusiform Gyrus, extending into Temporal Occipital Fusiform Cortex	36	-78	-12	5.46	2627	<0.001
	Left Temporal Fusiform Gyrus, extending into Occipital Fusiform Cortex	-38	-44	-22	5.69	1664	<0.001
	Left IFG, extending into left MFG	-44	16	28	4.08	748	0.005
HC > CD	mPFC, extending into left Frontal Pole	-22	40	-12	3.37	578	0.021

There were no activation clusters CD > HC.
HC: healthy controls; CD: patients with long-term remission of Cushing's Disease.
IFG: Inferior Frontal Gyrus; MFG: Middle Frontal Gyrus; SFG: Superior Frontal Gyrus; LOC: Lateral Occipital Cortex; ITG: Inferior Temporal Gyrus; mPFC: medial Prefrontal Cortex.

Supplementary Table 3. Activation clusters within amygdala ROI in response to emotional faces (vs scrambled faces)

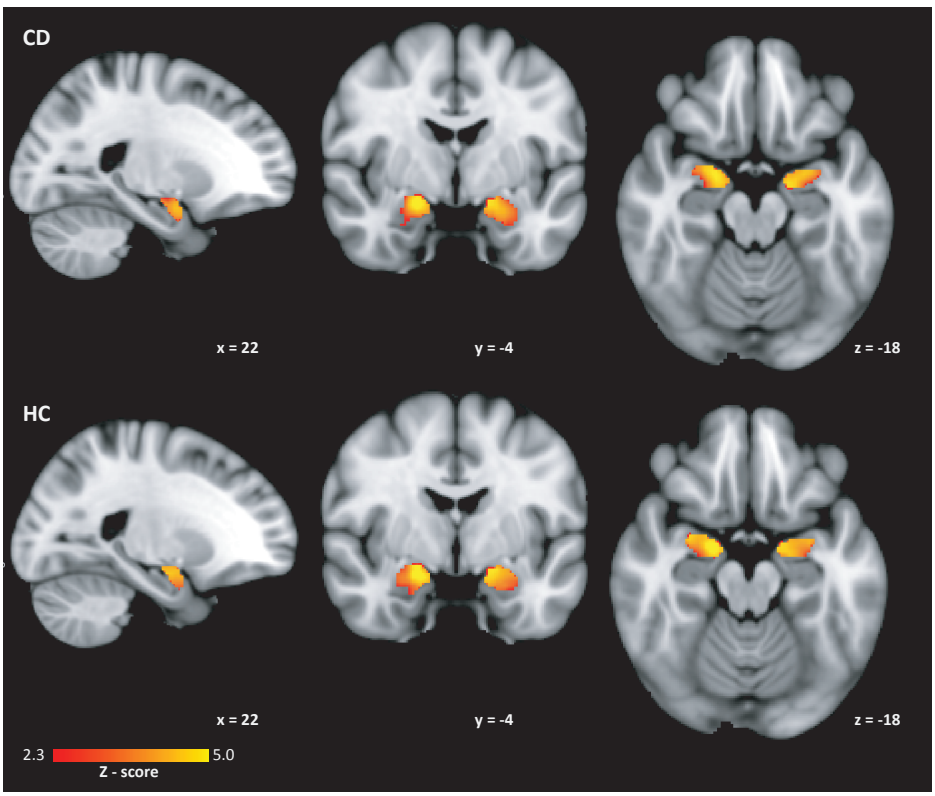
		MNI coordinates peak voxel					
	Region	**X**	**Y**	**Z**	**Max. Z value**	**# voxels**	**P-value**
HC	Right amygdala	20	-4	-16	5.41	256	0.002
	Left amygdala	-18	-4	-14	4.86	219	0.002
CD	Right amygdala	20	-4	-16	5.25	248	0.002
	Left amygdala	-16	-6	-16	4.94	206	0.003

There were no group differences in activation levels within this ROI.
HC: healthy controls; CD: patients with long-term remission of Cushing's Disease.

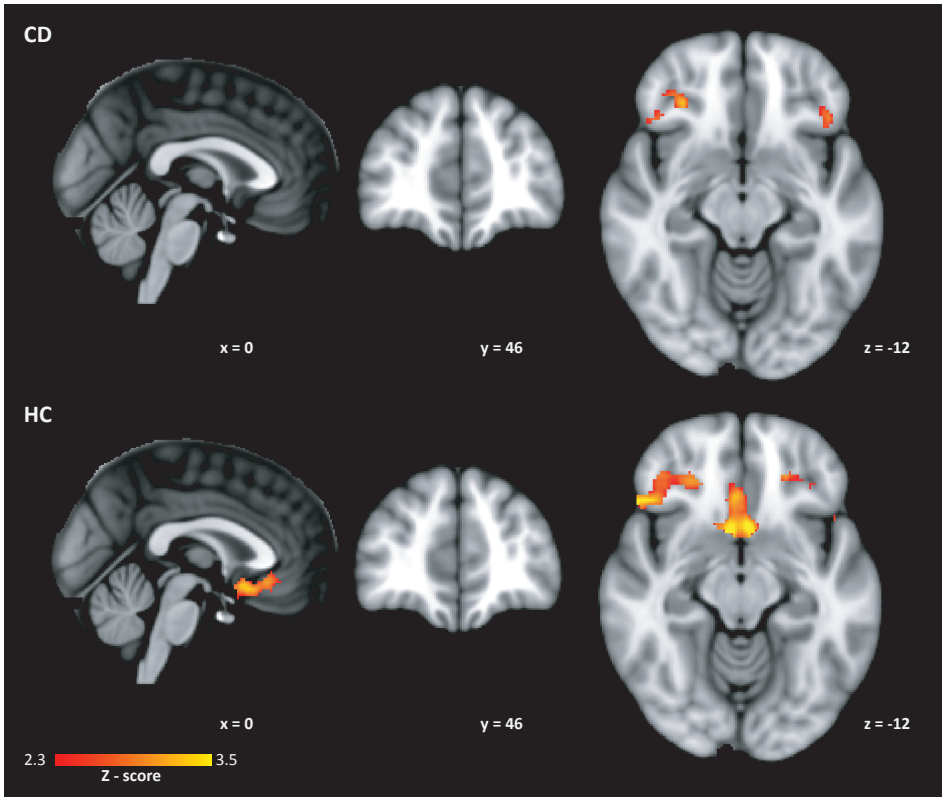
Supplementary Table 4. Activation clusters within mPFC ROI in response to emotional faces (vs scrambled faces)

		MNI coordinates peak voxel					
	Region	**X**	**Y**	**Z**	**Max. Z value**	**# voxels**	**P-value**
HC	Bilateral OFC, extending into subcallosal cingulate gyrus	28	6	-16	4.07	926	< 0.001
	Right Insular Cortex	36	22	0	4.26	769	< 0.001
	Left Insular Cortex	-30	26	4	3.94	277	0.020
CD	Right OFC, extending into right IFG	48	26	-2	4.04	498	0.002
	Left OFC	-38	32	-16	3.36	213	0.044
CD < HC	vmPFC	0	42	-12	3.2	274	0.021

There were no activation clusters CD > HC within this ROI.
HC: healthy controls; CD: patients with long-term remission of Cushing's Disease.
OFC: Orbitofrontal Cortex; IFG: Inferior Frontal Gyrus; vmPFC: ventromedial Prefrontal Cortex.



Supplementary Figure 1. Significant activation clusters related to viewing faces (emotional faces > scrambled faces) within the amygdala ROI. There were no differences in activation levels between CD-patients with long- term remission (CD) and control participants (HC). Significant clusters are superimposed on the template MNI_T1_152_1mm_brain. All images are displayed according to radiological convention: right in image is left in brain.



Supplementary Figure 2. Significant activation clusters related to viewing faces (emotional faces > scrambled faces) within the mPFC ROI. Significant clusters are superimposed on the template MNI_T1_152_1mm_brain. All images are displayed according to radiological convention: right in image is left in brain.

CHAPTER 5

Increased hair cortisol concentrations and BMI in patients with pituitary- adrenal disease on hydrocortisone replacement

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ABSTRACT

Background: Intrinsic imperfections and lack of reliable biomarkers preclude optimal individual dosing of hydrocortisone replacement in adrenal insufficiency (AI). However, the clinical relevance of optimal dosing is exemplified by frequently occurring side effects of over-replacement and the dangers of under-replacement. Cortisol in scalp hair has been identified as a retrospective biomarker for long-term cortisol exposure. We compared hair cortisol concentrations ($CORT_{hair}$) of patients with primary or secondary AI on replacement therapy with those of patient controls with a pituitary disease without AI (PC) and of healthy controls (HC).

Methods: In this cross-sectional study, hair samples and anthropometric data were collected in 132 AI patients (52 males), 42 PC (11 males), and 195 HC (90 males). The proximal 3 cm of hair were used. $CORT_{hair}$ were measured using ELISA.

Findings: $CORT_{hair}$ were higher in AI patients than in HC and PC ($P < 0.001$), and hydrocortisone dose correlated with $CORT_{hair}$ ($P = 0.04$). Male AI patients demonstrated higher $CORT_{hair}$ than female patients ($P < 0.001$). AI patients had higher body mass index (BMI) than HC ($P < 0.001$), and BMI correlated with $CORT_{hair}$ in the whole sample ($P < 0.001$).

Interpretation: Physiological hydrocortisone replacement is associated with increased COR T_{hair}. The association between $CORT_{hair}$ and BMI could suggest a mild overtreatment that may lead to adverse anthropomorphic side effects, especially in males. $CORT_{hair}$ measurements may be a promising additional tool to monitor cumulative hydrocortisone replacement in AI.

INTRODUCTION

Adrenal insufficiency (AI) in which the adrenal corticosteroid synthesis, i.e. cortisol production, is insufficient can be primary in case of pathology of the adrenal glands, or secondary in case of hypopituitarism. Patients with AI need replacement therapy with exogenous glucocorticoids, preferably hydrocortisone, which is synthetically produced cortisol (1). In persons with intact adrenal function around 5 to 10 mg of cortisol per m^2 of body surface area per day is produced (2), with increased requirements during stress. The corresponding chronic oral replacement dosage is 15–25 mg per day, usually divided in three dosages in an attempt to mimic the circadian rhythm of natural cortisol secretion, with a peak in the morning and a gradual decrease during the day and evening (1, 3). It is recommended that hydrocortisone replacement should be individualized, taking into account blood pressure, metabolic derangements and sense of well-being (4). Various maintenance dosing strategies have been published (5). However, it is likely that there will be large individual variation in substitution requirements in view of differences in cortisol sensitivity due to polymorphisms of the glucocorticoid receptor gene (6). Currently available cortisol measurements in plasma, urine or saliva do not reflect cortisol action at tissue level. In accordance, plasma and salivary cortisol concentrations vary considerably between patients receiving hydrocortisone replacement, limiting the possibility to titrate individual hydrocortisone doses upon single plasma, or salivary measurements (7). A method to retrospectively assess cortisol for longer periods of time is the analysis of cortisol in scalp hair (8). As hair grows approximately one cm per month (9), a hair sample of for example three cm represents the long-term cortisol concentration of three months. Hydrocortisone is identical to human cortisol and has been shown to be measureable in scalp hair (8, 10).

Hair cortisol levels ($CORT_{hair}$) have repeatedly been associated with body mass index (BMI) and increased risk of metabolic syndrome and cardiovascular disease in populations with endogenous cortisol metabolism (11-15). Until now, there is very limited data on the clinical utility of $CORT_{hair}$ measurements in patients with hydrocortisone replacement as is the case in AI. A recent study by Gow et al. demonstrated that hydrocortisone dose was significantly positively associated with $CORT_{hair}$ in patients with primary AI (10). Furthermore, they demonstrated a significant difference in $CORT_{hair}$ in male subjects between patients and controls, but no statistically significant difference in females. In addition, they did not observe a difference between male and female patients' $CORT_{hair}$. Thus, this study provided data indicative of a potential gender dependent effect in $CORT_{hair}$ in patients on hydrocortisone replacement. However, it should be acknowledged that this study included only 13 male patients *vs.* 80 female patients, which limits the generalizability of the results.

Therefore, we aimed to compare $CORT_{hair}$ in a large cohort of patients with primary and secondary AI on hydrocortisone replacement therapy (AI patients) with $CORT_{hair}$ of control patients with a pituitary disease but no hydrocortisone replacement therapy (PC) and healthy controls (HC). Furthermore, we aimed to explore possible determinants of $CORT_{hair}$ in hydro-

cortisone treated AI patients, i.e. self-reported hydrocortisone intake, sex, age, and weight. We hypothesized that AI patients would have higher $CORT_{hair}$ than PC and HC, and that AI patients show side effects associated with high cortisol levels. Moreover, we hypothesized that $CORT_{hair}$ are associated with doses of hydrocortisone replacement and BMI.

SUBJECTS AND METHODS

Study design

This study was designed as a cross-sectional assessment of patients seen at the outpatient clinic of the department of Endocrinology of the Leiden University Medical Center. This study was conducted between July 2012 and January 2014. Hair samples were collected and patients were asked to fill out two short self-developed questionnaires: one questionnaire about their hair treatment, and one questionnaire about their hydrocortisone intake (i.e. self-reported daily dose, time of intake, frequency of increasing/decreasing hydrocortisone dose) and/or the potential usage of other exogenous glucocorticoids. Clinical data of patients were obtained from their medical records.

Participants

Patients

We included two groups of patients: group I) patients with primary or secondary adrenal insufficiency using hydrocortisone (AI patients), and group II) patient controls (PC) with a pituitary disease not using hydrocortisone. A total of 184 patients were willing to participate. Patients could not participate in case of insufficient hair growth at the posterior vertex of the scalp. Ten patients were excluded from the analysis because of interpretative difficulty of their chronic steroid replacement scheme; three had high levels probably due to a hydrocortisone stress scheme for Addison's crisis in the three months prior to hair collection, three patients were excluded because of $CORT_{hair}$ >3 SD with no clear explanation, and four patients were excluded due to debatable AI diagnosis and inconsistent hydrocortisone use. The final sample comprised a total of 174 patients (i.e. 132 AI patients and 42 PC). Primary AI had been diagnosed by very low early morning cortisol concentrations (<120 nmol/l) or insufficient stimulation following ACTH test (below 550 nmol/l) usually in the presence of positive adrenal auto-antibodies or an alternative explanation. Secondary adrenal insufficiency was preferably diagnosed using an insulin tolerance test (ITT), or if contra-indicated, a CRH test using the same cut-off as for ACTH stimulation. Pituitary hormone replacement was prescribed dependent on the results of the annual evaluation of pituitary functions. In case of AI, hydrocortisone was prescribed (usually 20 mg/d divided into 3 dosages, with adjustments if clinically judged necessary by the treating physician) together with advices to increase the

hydrocortisone dose in case of exposure to severe somatic and/or psychological stressors. In case of other hormone deficiencies, patients were substituted accordingly.

Healthy controls

To compare $CORT_{hair}$ between patients and healthy individuals, we used a group of 195 healthy controls (HC) previously described elsewhere (8).

The study was approved by the local ethics committee. All patients and controls gave written informed consent.

Hair cortisol assessment

A lock of approximately 150 hairs was cut as close to the scalp as possible from the posterior vertex. For analysis, the most proximal three cm of hair were used, corresponding to the most recent three months. Hair sample preparation and analysis has been described previously (8). In short, a minimum of 10 mg of hair was weighed and cut into small pieces in a glass vial. Extraction of cortisol took place in 1 mL of methanol for 16h at 52^{o}C while gently shaking. After extraction, the methanol was transferred to another vial and evaporated under a constant stream of nitrogen. The samples were dissolved in 250 µL of phosphate buffered saline (PBS, pH 8.0) for analysis. A commercially available ELISA Kit for salivary cortisol (DRG GmbH, Marburg, Germany) was used to measure cortisol levels. A correction factor was applied to the results to account for the potential influence of different hair weights. Cross reactivity of other steroids with the kit's antibodies was reported as follows: Corticosterone (29.00%), Cortisone (3.00%), 11-Deoxycortisol (<1.00%), 17-OH Progesterone (<0.50%), other hormones (<0.10%). Intra-assay variation was below 5% and the inter-assay variation below 8% as reported by the supplier. The recovery of the assay was described previously (8).

Statistical analysis

SPSS 20.0 for Windows was used for statistical analysis. Differences in demographic information between groups were tested with One-Way-ANOVAs and Pearson Chi Square tests. After logarithmic transformation, $CORT_{hair}$ were normally distributed. Analyses on $CORT_{hair}$ and differences between groups were performed by means of univariate general linear models. If groups differed on age, sex, BMI, or hair treatment (see Table 1 and Table 2), analyses on group differences were adjusted accordingly. For analyses of the etiologies of hydrocortisone use, post-hoc tests were applied. Pearson and spearman correlations were used for correlation analyses, depending on normality of the distribution. $CORT_{hair}$ are provided in pg/mg and are reported as median (Mdn) and interquartile range (IQR).

RESULTS

Participant characteristics (Table 1)

132 AI patients, 42 PC, and 195 HC were included in the analysis. The frequency of using glucocorticoid containing medication (other than hydrocortisone or maintenance dose) was 14.9% and did not differ between AI patients and PC (P = 0.26). Of these, 12.6% used one, and 2.3% used two kinds of glucocorticoid containing medication. The most frequent used products were ointments (n = 8) and inhalation aerosols (n = 8). Five patients used nasal spray, and one patient had received an injection into a joint. Patients that used externally applied glucocorticoid containing medication did not show different $CORT_{hair}$ than non-applying patients and were therefore not excluded (P = 0.75). The mean disease duration was not significantly different between AI patients (18.33 ± 13.54 years) and PC (15.06 ± 10.30 years), P = 0.16). Presence of hypertension (defined as either blood pressure above 140/90 or use of antihypertensive medication) and presence of diabetes mellitus (defined as use of oral medication and/or insulin injection) was not different between AI patients and PC, and in AI patients, frequencies of hypertension and diabetes mellitus were comparable between genders. Both AI and PC showed higher frequencies of diabetes mellitus than HC (both P < 0.05). Hypertension data were not available for HC.

Table 1. Baseline characteristics of patients, patient controls and HC

	AI patients (n = 132)	PC (n = 42)	HC (n = 195)	P-value[1]	P-value[2]	P-value[3]
Age	54.84 (14.99)	49.07 (12.94)	36.17 (12.23)	**0.05**	**0.001**	**0.001**
Sex (male)	52 (39.4%)	11 (26.2%)	90 (46.2%)	0.12	0.23	**0.02**
BMI	27.80 (5.12)	28.70 (7.45)	24.34 (3.85)	0.95	**0.001**	**0.001**
Use of exogenous glucocorticoids#	15 (11.5%)	2 (4.9%)	NA	0.21	NA	NA
Hypertension	56 (43.8%)	24 (60.0%)	NA	0.07	NA	NA
Diabetes mellitus	21 (9.2%)	4 (9.8%)	5 (2.6 %)	0.92	**0.008**	**0.029**
Hair dyed	42 (36.2%)	16 (42.1%)	37 (19.0%)	0.52	**0.001**	**0.002**
Hair bleached	13 (9.9%)	9 (22.0%)	13 (6.7%)	**0.04**	0.29	**0.002**
Hair permed	2 (1.5%)	3 (7.3%)	2 (1.0%)	**0.05**	0.69	**0.01**
Use hairproduct	66 (50.0%)	22 (53.7%)	90 (46.4%)	0.68	0.52	0.40
Frequency hair wash > 3 times/week	46 (35.1%)	17 (41.5%)	143 (74.1%)	0.46	**0.001**	**0.001**

P-value[1]: comparison between AI patients and PC, P-value[2]: comparison between AI patients and HC, P-value[3]: comparison between PC and HC

Data are presented as mean (standard deviation), and as n (valid percentage). AI, adrenal insufficiency; PC, patient control group; HC, healthy control group; BMI, Body Mass Index; NA, not applicable; #, use of other external glucocorticoids (besides hydrocortisone).

Table 2. Baseline characteristics of male and female AI patients

	Males (n = 52)	Females (n = 80)	P-value
Age	55.94 (16.01)	54.13 (14.35)	0.50
BMI	27.57 (3.85)	27.95 (5.80)	0.68
Duration of follow-up (years)	17.87 (12.69)	18.62 (14.11)	0.76
Daily hydrocortisone dose (mg)	21.58 (4.98)	20.39 (4.21)	0.15
Daily hydrocortisone dose mg/kg	0.25 (0.07)	0.27 (0.07)	0.12
Daily hydrocortisone dose mg/BSA	10.35(2.54)	10.84 (2.27)	0.26
Use of external glucocorticoids #	5 (10.0%)	10 (12.5%)	0.66
Hypertension	23 (46.9%)	33 (41.8%)	0.57
Diabetes Mellitus	4 (8.0%)	8 (10.0%)	0.70
Hair dyed	0	42 (58.3%)	**0.001**
Hair bleached	0	13 (16.5%)	**0.002**
Hair permed	1 (1.9%)	1 (1.3%)	0.76
Use hairproduct	19 (36.5%)	47 (58.8%)	**0.01**
Frequency hair wash			**0.03**
< 2 times/week	28 (53.8%)	57 (72.2%)	
> 3 times/week	24 (46.2%)	22 (27.8%)	

Data are presented as mean (standard deviation), and as n (valid percentage). #: use of other external glucocorticoids (besides hydrocortisone); BMI, Body Mass Index; BSA, body surface area.

$CORT_{hair}$ in AI patients, PC, and HC (Figure 1a-b)

Analyses showed a significant difference in $CORT_{hair}$ between the three groups, F(2, 343) = 35.39, P < 0.001, adjusted for age, gender, and dyeing of the hair. Post-hoc tests indicated that AI patients had higher $CORT_{hair}$ (33.89, 14.82 – 89.29) than PC (13.66, 6.22 – 26.58), P= 0.001, and HC (10.07, 3.52 – 17.83), P < 0.001, and that PC had higher $CORT_{hair}$ than HC, P= 0.04. In AI

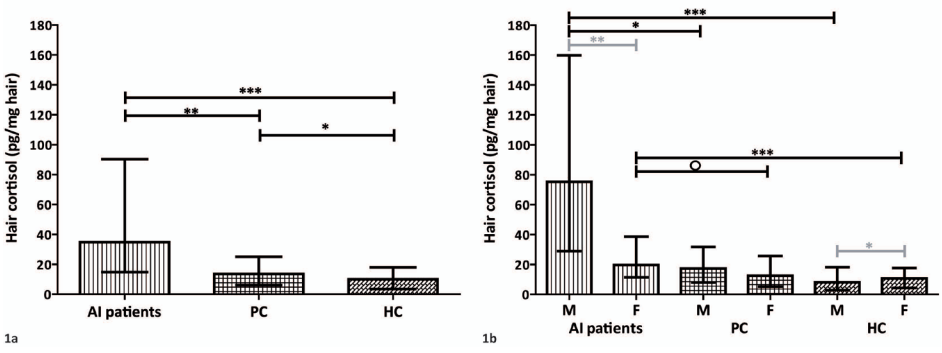

Figure 1. Median and IQR of $CORT_{hair}$. AI, adrenal insufficiency; PC, patient control group; HC, healthy control group. Untransformed data are shown. 1a) $CORT_{hair}$ of AI patients, PC, and HC. 1b) $CORT_{hair}$ for AI patients, PC, and HC, stratified for sex. *** = P < 0.001; ** = P < 0.01; * = P < 0.05, ○ = P < 0.1. Black lines represent differences between the participant groups, whereas grey lines represent sex differences within each participant group.

patients, 35.6% (61.5% males, 18.8% females) presented with $CORT_{hair}$ above our lab-internal cut-off for normal, as did 7.1% (9.1% males, 6.5% females) of PC and 3.1% (5.6% males, 1.0% females) of HC. Our lab-internal upper limit of normal is 52 pg/mg. For determination, we restricted our group of healthy controls to the ones with a BMI between 18.5 and 30.0, and used the 97.5 percentile as cut-off value.

In AI patients, men had significantly higher $CORT_{hair}$ (75.25, 28.91 – 159.81) than women (19.59, 11.49 – 38.49), $F(1, 112) = 8.17$, $P = 0.005$), adjusted for age and dyeing of the hair. No gender differences were observed in $CORT_{hair}$ in PC. In HC, females showed higher $CORT_{hair}$ than males, $F(1, 191) = 5.45$, $P = 0.02$. Stratified analysis for gender revealed that male AI patients had higher $CORT_{hair}$ than male PC and HC ($P = 0.02$ and $P < 0.001$, respectively), whereas for female AI patients, $CORT_{hair}$ was trend-significantly higher than in female PC ($P = .07$) and significantly higher than in female HC ($P < 0.001$). Males in the PC group did not show different $CORT_{hair}$ from males in the HC group, and females in the PC group had not different $CORT_{hair}$ compared to females in the HC group (all $P > 0.1$). Within AI patients, no difference in $CORT_{hair}$ was found for the various etiologies of AI.

Correlation between hydrocortisone dose and hair cortisol levels (Figure 2)

Self-reported daily hydrocortisone maintenance dose correlated with $CORT_{hair}$ ($\rho = 0.18$, $P = 0.04$). Stratification for gender showed that this correlation was primarily driven by the female AI patients ($\rho = 0.24$, $P = 0.04$), whereas the correlation was not significant in male AI patients. Neither incidental higher and/or lower hydrocortisone dosages nor the morning (peak) dose of hydrocortisone ($\rho = 0.15$, $P = 0.09$) were related to $CORT_{hair}$. The self-reported

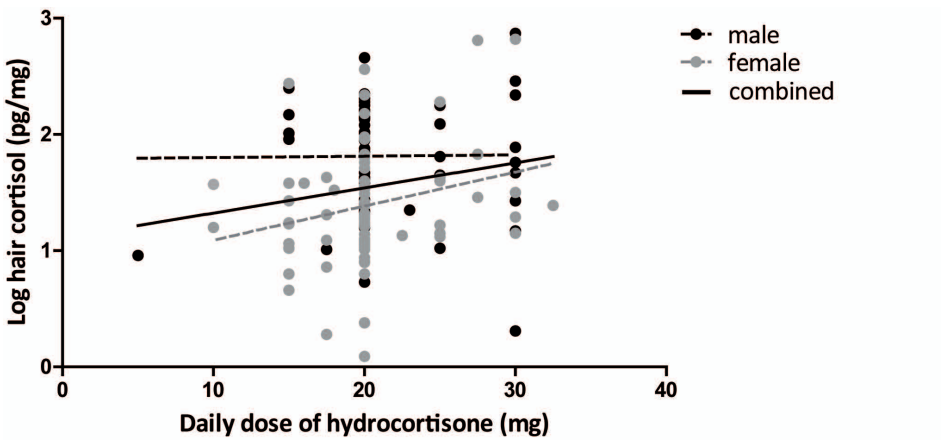

Figure 2. The relationship between daily hydrocortisone dose (mg/day) and $CORT_{hair}$ (pg/mg), $\rho = 0.18$, $P = 0.04$, as indicated with the black solid line, which is the regression line of the group analysis. Analyses stratified for sex show that this effect was driven by the female AI patients (grey; $\rho = 0.24$, $P = 0.04$), whereas no effect was observed for the male AI patients (black; $\rho = -0.04$, $P = 0.79$). $CORT_{hair}$ are shown on a log scale.

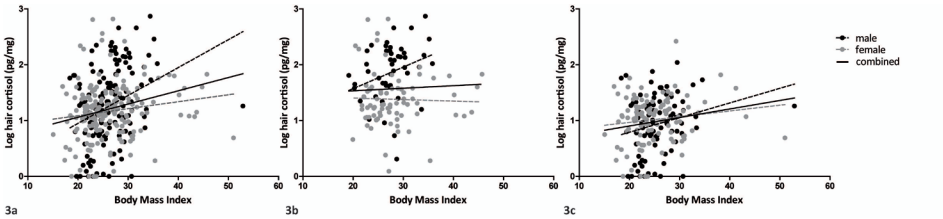

Figure 3. The relationship between BMI and $CORT_{hair}$. 3a) The association between BMI and $CORT_{hair}$ for all participants was significant ($\rho = 0.24$, $P < 0.001$, black solid line); stratification for sex did not change the results ($\rho = 0.35$, $p < 0.001$ for male participants (black); $\rho = 0.18$, $P = 0.02$ for female participants (grey). 3b) In only the adrenal insufficiency (AI) patients, the association between BMI and $CORT_{hair}$ was not significant; $\rho = 0.11$, $P = 0.23$ (black solid line). Stratification for sex rendered a significant correlation for male AI patients ($\rho = 0.34$, $P = 0.02$, black) but no association for female AI patients ($\rho = 0.04$, $P = 0.73$, grey). 3c) In the control persons, the association did reach significance ($\rho = 0.14$, $P = 0.04$, black solid line). Stratified analyses showed that this effect was driven by the male controls ($\rho = 0.24$, $P = 0.02$, black) but was not significant for female controls ($\rho = 0.10$, $P = 0.31$, grey).

daily hydrocortisone dose in mg/kg or mg/m^2 was not related to $CORT_{hair}$ and stratification for sex did not render different results.

Correlations between anthropometrics and hair cortisol levels (Figure 3)

As indicated in Table 1, BMI differed significantly between AI patients, PC and HC ($F2, 327) = 23.90$, $P < 0.001$. Post-hoc tests revealed that the BMI of AI and PC patients was significantly higher compared to HC ($P < 0.001$), but there was no significant difference between AI and PC. For the whole group of participants, BMI showed a significant correlation with $CORT_{hair}$ ($\rho = 0.24$, $P < 0.001$). Stratification for sex and participant group revealed a significant correlation between BMI and $CORT_{hair}$ for male AI patients ($\rho = 0.34$, $P = 0.02$), but not for female AI patients nor for male or female PC or HC. Waist-to-hip ratio (WHR) information was only available in a subset of 50 AI patients, 12 PC, and 45 HC. WHR was not different between the groups. In the whole sample of participants, WHR and $CORT_{hair}$ correlated significantly ($r = 0.20$, $P = 0.04$). WHR and waist circumference were related to self-reported dose in mg/kg ($r = -0.3$, $P = 0.04$, and $r = -0.58$, $P < 0.001$, respectively) and to self-reported dose in mg/BSA ($r = -0.36$, $P = 0.01$, and $r = -0.64$, $P < 0.001$, respectively), but were not related to the total self-reported daily hydrocortisone maintenance dose ($r = 0.11$, $P = 0.46$, and $r = 0.19$, $P = 0.17$, respectively).

DISCUSSION

The present study showed that patients using hydrocortisone replacement for AI demonstrate higher $CORT_{hair}$ than pituitary patients and healthy controls with an intact HPA-axis. Furthermore, a gender-effect was identified, with male patients with AI demonstrating higher $CORT_{hair}$ than females, without differences in self-reported hydrocortisone intake. Intriguingly, this gender effect seems to be specific for hydrocortisone use, since it is not present in controls with an intact HPA-axis. In female patients, higher self-reported hydrocortisone intake was associated with higher $CORT_{hair}$, whereas this association was not found in male patients who demonstrated on average higher $CORT_{hair}$ even in the lower dose range.

In male, but not female AI patients, higher $CORT_{hair}$ were associated with higher BMI. This relation suggests that high $CORT_{hair}$ may reflect chronic overexposure to hydrocortisone, at least in male patients. However, further study is required to understand the role of gender in the determination of cortisol levels in hair and to confirm whether $CORT_{hair}$ are indeed representative for corticosteroid exposure in the rest of the organs. Furthermore, it is still unclear how exactly cortisol, and hence hydrocortisone, is incorporated into scalp hair (16). Therefore, the question remains whether it is the cumulative amount of cortisol or the cortisol peak that is most influential on $CORT_{hair}$. In our study, total dose appears to be associated with $CORT_{hair}$, and not a single/maximum dose. In contrast, the three patients who received a hydrocortisone bolus for an Addison crisis had extremely high values and were excluded from the study (data not shown), suggesting a role for a supraphysiological peak in determination of $CORT_{hair}$. In contrast to the positive correlation between the absolute hydrocortisone dose and $CORT_{hair,}$ we found no relation between body weight-adjusted dose and $CORT_{hair,.}$ This is an interesting finding, since previous research has reported that clearance of hydrocortisone in serum is faster in obese patients, and that adjusting the dose for body weight may be beneficial for the patient (5, 17). However, the current study may imply that tissue exposure following ingestion of hydrocortisone (at a physiological level) is independent of distribution volume, i.e. weight, at least for these patient groups as measured by $CORT_{hair}$, and thus questions the need to increase the hydrocortisone dose in obese patients. This is in accordance with recent guidelines pointing to no adjustment for weight (except for children) (3). Male patients reached higher $CORT_{hair}$ with considerably lower hydrocortisone dosages than female patients. This "higher sensitivity" to hydrocortisone is in accordance with the positive association between $CORT_{hair}$ and BMI in male patients. A possible explanation for this higher sensitivity in male patients might be that men seem to have lower corticosteroid binding globulin (CBG) levels while total cortisol levels are comparable to women's total cortisol (18). This may result in higher free cortisol levels in men upon hydrocortisone intake. As free cortisol is thought to be the cortisol fraction which is incorporated in hair (19), this might explain the sex difference found in our study and in the study of Gow and colleagues (10). However, the clearly increased $CORT_{hair}$ suggest that in general patients with AI are chronically over-replaced, despite prescribed hydrocortisone replacement dosages aiming at mimicking

a "physiological" level. A higher daily hydrocortisone dose has been previously linked to a more adverse cardiometabolic risk profile, characterized by higher BMI (20). Steroid excess-related morbidity is well known from AI cohorts treated with higher doses, resulting in the awareness to replace hydrocortisone with the lowest dose possible, generally regarded to as a daily hydrocortisone dose of 20 mg (21-22). It is intriguing that AI patients treated with the currently advised low hydrocortisone dose have clearly increased $CORT_{hair}$ and additionally present with steroid-related side effects, such as increased BMI.

It appears unlikely that an increased perceived stress of being a patient influences $CORT_{hair}$ in this study. Some AI patients are known to occasionally increase their hydrocortisone doses in situations of increased psychological stress (23), which might result in higher $CORT_{hair}$. In population studies, $CORT_{hair}$ has been associated with perceived stress (24-26), but if this was the case in the present study, the increased stress of being a patient should then also be present in our PC group. However, $CORT_{hair}$ between PC and HC were comparable.

Several strengths and limitations of the present cross-sectional study need to be mentioned. In total, we included a considerable number of patients, which enabled us to examine $CORT_{hair}$ of patient groups with pituitary diseases due to different etiologies. Furthermore, we included a patient control group with a pituitary disease and normal adrenal function. All concurrent pituitary insufficiencies were treated, but we do acknowledge that, such as hydrocortisone replacement therapy, intrinsic imperfections of hormone replacement are also an important issue for gonadal steroids, thyroid hormone, and growth hormone replacement.

Besides the demonstrated association between $CORT_{hair}$ and anthropometrics, a considerable amount of studies demonstrated the association between high $CORT_{hair}$ and psychological symptoms (25). Furthermore, in a recent study it was demonstrated that a higher hydrocortisone intake in patients with primary adrenal insufficiency was associated with more impairments in quality of life, psychological morbidity, and maladaptive personality traits (27). For future research, it would be interesting to assess patients' perceived well-being in relation to $CORT_{hair}$.

In conclusion, patients on hydrocortisone replacement therapy have elevated $CORT_{hair}$, a finding which is predominantly present in male patients. Despite a low dose of on average 21 mg/day only 64.4% of patients had $CORT_{hair}$ in the normal range. This study provides important data on the fact that contemporary steroid replacement still results in clear supra-physiological (hair) cortisol levels, especially in males. However, it needs to be confirmed that $CORT_{hair}$ reflects cortisol (over)exposure in other organs of the body in exogenously treated patients, or that the incorporation of $CORT_{hair}$ is different from the reference population with normal HPA-axis. Next, it needs to be established which are safe, gender-specific $CORT_{hair}$ for patients to allow for the monitoring of hydrocortisone dose while avoiding the dangers of under- and over-replacement.

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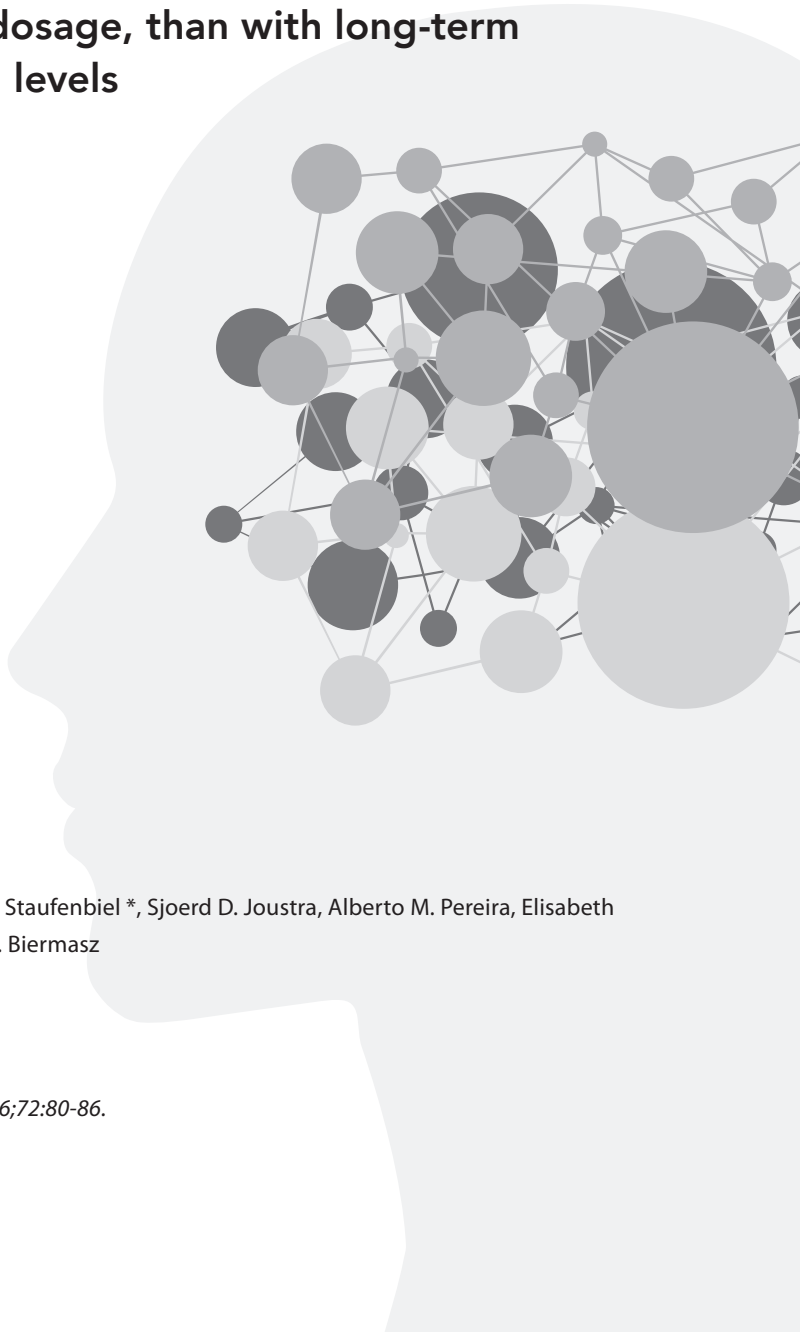
CHAPTER 6

Quality of life in patients with adrenal insufficiency correlates stronger with hydrocortisone dosage, than with long-term systemic cortisol levels



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ABSTRACT

In patients with adrenal insufficiency (AI) a higher hydrocortisone intake has been associated with more impairment in Quality of Life (QoL). Irrespective of age, sex and severity of AI the dosage of hydrocortisone is titrated around 20 mg/D in all patients with AI based on physical and mental signs and symptoms. However, until now it is unknown whether these QoL impairments are related to increased systemic cortisol exposure. Measurement of hair cortisol levels ($CORT_{hair}$) can be used to assess chronic systemic cortisol exposure. This study aimed to explore whether QoL in patients with AI is associated with $CORT_{hair}$ and daily hydrocortisone intake. We performed a cross-sectional study in 120 patients with AI on stable hydrocortisone replacement, in whom hair samples and QoL data were collected. $CORT_{hair}$ were measured with ELISA, and QoL was assessed with validated questionnaires (SF-36, EQ-5D, HADS, MFI-20). Patients reported impairments in 14 of 15 QoL subscales ($P < .001$). More impairments in physical aspects of QoL correlated with higher $CORT_{hair}$ and higher daily hydrocortisone intake ($P < .05$), an effect that was more pronounced in female patients. Regression analyses including both $CORT_{hair}$ and hydrocortisone intake revealed a significant negative contribution of higher hydrocortisone intake on physical aspects of QoL ($P \leq .046$), whereas no significant contribution was found for $CORT_{hair}$.

The present study showed that patients with AI report several impairments in QoL which are associated with hydrocortisone intake, and to a lesser extent reflected by chronic systemic cortisol exposure as measured by hair cortisol. This suggests that QoL impairments in patients with AI are not per se the effect of prolonged exposure to elevated systemic cortisol levels.

INTRODUCTION

Adrenal insufficiency (AI) is treated with glucocorticoid replacement therapy, usually 20 to 30 mg of hydrocortisone daily, divided into three dosages (10-15 mg in the morning, 5-10 mg in the afternoon, 4-5 mg in the evening), in order to mimic the natural circadian secretion of cortisol (1). However, even when patients with primary AI are in a stable medical condition, they report impaired quality of life (QoL) (2-6). In addition, in patients with secondary AI due to pituitary disease, hypopituitarism was found to be an important predictor of QoL impairments (7-9). It has been suggested that these QoL impairments are associated with intrinsic imperfections in glucocorticoid replacement therapy, and therefore, it is advised that hydrocortisone replacement should be individualized (10). For instance, there is large individual variation in sensitivity to cortisol, which is partly explained by polymorphisms of the glucocorticoid receptor gene (11). However, determining an optimal hydrocortisone replacement dose is complicated by the lack of reliable chronic parameters, and as a result many patients may be chronically under- or overtreated with potential paramount consequences for well-being and health.

Until now, it is not well established whether QoL is affected by the degree of cortisol exposure (i.e. adequacy of hydrocortisone replacement) in patients with AI. In a single study, authors investigated plasma cortisol day curves and well-being in a small sample of seven patients with AI and demonstrated that subphysiological cortisol levels correlated with lower well-being (12). Other studies examined the relation between the dosage and intake scheme of glucocorticoid replacement therapy and QoL, and demonstrated that in patients with AI, QoL was inversely correlated with the hydrocortisone dose (5;13). Importantly, associations between hydrocortisone intake and QoL do not provide any information about causality, since it might be that high cortisol levels cause QoL impairments, but it might also be that patients with worse QoL need more hydrocortisone.

Addressing this relationship is further complicated by the difficulty of adequately measuring cortisol levels throughout the day, since cortisol levels vary depending on different treatment regimens (i.e. varying hydrocortisone doses, as well as differences in timing, absorption, and metabolism of hydrocortisone), and currently available cortisol measurements (i.e. plasma, urinary, salivary) are limited to short-term assessments.

A promising method to assess cortisol for prolonged periods of time is the analysis of cortisol levels in scalp hair ($CORT_{hair}$) (14;15). We (and others) recently assessed the use of this measure in AI patients treated with exogenous hydrocortisone. Patients with AI have increased levels and hydrocortisone intake has been found to correlate with $CORT_{hair}$ (16;17). A significant gender effect has been reported in $CORT_{hair}$ in patients with AI treated with glucocorticoid replacement therapy, with male patients demonstrating higher $CORT_{hair}$ than females while using the same dose of hydrocortisone (16;17).

In the present study, we aimed to explore whether $CORT_{hair}$ is correlated with QoL. We first compared QoL in patients with stable treatment for AI with QoL in healthy controls. Second,

we examined potential correlations between QoL, $CORT_{hair}$, and daily hydrocortisone intake as another parameter to assess cortisol exposure.

PATIENTS AND METHODS

Patients

Scalp hair samples were collected of 132 patients with primary or secondary AI on hydrocortisone replacement from the Endocrinology out-patient clinic of the Leiden University Medical Center (cohort previously described in (17)). Of this group, nine patients did not fill out QoL questionnaires and three patients filled out less than 75% of the questionnaires and were therefore excluded from the analysis. Thus, 120 patients with longstanding AI on a stable dose were included in the present study. Primary AI had been diagnosed by very low early morning cortisol concentrations (<120 nmol/l) or insufficient stimulation following ACTH test (below 550 nmol/l) usually in the presence of positive adrenal auto-antibodies or an alternative explanation. Secondary adrenal insufficiency was preferably diagnosed using an insulin tolerance test, or if contra-indicated, a CRH test using the same cut-off as for ACTH stimulation. Pituitary hormone replacement was prescribed dependent on the results of the annual evaluation of pituitary functions. In case of AI, hydrocortisone was prescribed (usually 20 mg per day divided into three dosages, adjusted at the discretion of the treating physicians) together with the advice to increase the hydrocortisone dose in case of exposure to severe somatic and psychological stressors.

Comparison QoL data of 437 healthy controls were derived from a previous study from our department (18).

The local ethics committee approved this study. All patients gave written informed consent.

QoL assessment

QoL was assessed with the following four validated questionnaires:

The *Short-Form 36 (SF-36)* assesses functional status and general well-being and consists of 36 items covering nine health concepts: 1) physical functioning, 2) social functioning, 3) role limitation (physical), 4) role limitation (emotional), 5) mental health, 6) vitality, 7) pain, 8) general health perception, and 9) general perception of change in health. Scores are expressed on a 0–100 scale, and higher scores indicate better QoL (19).

The *EuroQoL-5D (EQ-5D)* assesses the current health status reflected in five health dimensions; 1) mobility, 2) self-care, 3) usual activities, 4) pain/discomfort, and 5) anxiety/depression. Scores are expressed on a 1-3 scale per dimension, with higher scores indicating worse QoL. Also a visual analogue scale is included ranging from 0 to 100 for recording an individual's rating for their current health-related well-being, with higher scores indicating a better health status (20).

The *Hospital Anxiety and Depression Scale (HADS)* assesses both anxiety and depressive symptoms and consists of 14 items on a 4-point scale. Higher scores indicate more severe anxiety and depressive symptoms (21;22).

The *Multidimensional Fatigue Inventory (MFI-20)* consists of 20 statements assessing fatigue on a five-point scale covering five dimensions; 1) general fatigue, 2) physical fatigue, 3) reduced activity, 4) reduced motivation, and 5) mental fatigue. Scores vary from 0-20; with higher scores indicating greater fatigue (23).

QoL of healthy controls

QoL data of healthy controls were previously collected at our department (18). The EuroQoL-5D and two subscales of the Short-Form 36 (i.e. mental health, vitality) were not assessed in this group of healthy controls. QoL data of 437 healthy controls (136 males) with a mean age of 50.9 ± 13.6 years were available and the total group was used for comparison.

Hair collection, preparation, and analysis

A lock of approximately 150 hairs from the posterior vertex was cut as close to the scalp as possible. The hair samples were taped to paper and stored in the dark at room temperature until further analysis. One cm represents the average cortisol concentrations of one month (15), since it is assumed that hair grows one cm per month, with a range of 0.6 – 1.4 cm/month (24).

Hair samples are specifically taken from the vertex region of the scalp because its most uniform growth pattern and phase (25;26), and importantly, has been specifically been validated for cortisol with the lowest mean coefficient of intra-individual variation (27). For analyses, the most proximal 3 cm of hair was used, corresponding to the most recent 3 months. A minimum of 10 mg of hair was weighed and cut into small pieces. For extraction, 1 mL of methanol was added and the samples were incubated for 16h at 52^{0}C. After extraction, the methanol was transferred to another vial and evaporated under a constant stream of nitrogen. The samples were dissolved in 250 µL of phosphate buffered saline (PBS, pH 8.0). A commercially available ELISA Kit for salivary cortisol (DRG GmbH, Marburg, Germany) was used to measure cortisol levels. The procedure has been described in detail elsewhere (14). Our laboratory internal upper limit of normal is 52 pg/mg.

Statistical analyses

Data were analyzed using PASW Statistics version 20.0 (SPSS Inc., Chicago, IL). $CORT_{hair}$ were reported as median and interquartile ranges (IQR). Other data were presented as mean±SD, unless mentioned otherwise. After logarithmic transformation, $CORT_{hair}$ were normally distributed. The primary analysis comprised the comparison of QoL of patients with AI to healthy controls by using independent sample t-tests when data were normally distributed and Mann-Whitney U tests when data were not normally distributed. In order to evaluate

whether the previously found gender effect in $CORT_{hair}$ is reflected in QoL, this analysis was also performed after stratification for gender.

The secondary analysis comprised the assessment of the potential association between QoL, $CORT_{hair}$, and daily hydrocortisone intake. Partial correlations were calculated between QoL and $CORT_{hair}$ and daily hydrocortisone intake, adjusted for age and gender. Subsequently, groups were stratified for gender and partial correlations were calculated between QoL and $CORT_{hair}$ and daily hydrocortisone intake, adjusted for age. Regression analyses including linear and quadratic terms were used to examine possible u-shaped associations. Furthermore, regression analyses including both $CORT_{hair}$ and daily hydrocortisone intake were used to differentiate between the contributions of these two factors. Because of the exploratory nature of these analyses, adjustment of the level of significance for multiple testing was not performed, and the level of significance was set at $P < .05$.

RESULTS

Patient characteristics

A total of 120 patients with longstanding AI (46 males) with a mean age of 55.0 ± 14.7 years were included in the analyses. The duration of follow-up was on average 18.5±13.3 years, with a median of 15.8 years (IQR: 8.1-28.9). Patients used a mean daily dose of 21.1 ± 4.5 mg. In the whole group of patients, 34% presented with $CORT_{hair}$ above our lab-internal cut-off for normal (52 pg/mg). Of the males, 59% demonstrated $CORT_{hair}$ higher than the lab-internal cut-off, in contrast to 19% of the females ($P < .001$). As previously reported (17), also in the present study male patients demonstrated higher $CORT_{hair}$ than female patients (75.3 (26.2 - 150.1) vs. 19.7 (11.6 - 38.5), $P < .001$). Furthermore, female patients dyed or bleached their hair more and used hair products more frequently than male patients (all $P \leq .03$) (Table 1). Daily hydrocortisone intake and $CORT_{hair}$ showed a significant, but modest correlation ($r = 0.185$, $P = .047$).

To evaluate whether there were differences in $CORT_{hair}$ between different etiologies of AI, five groups were formed: 1) AI due to previous treatment for Cushing's disease (n = 18), 2) other functioning pituitary adenomas (n = 14, including acromegaly (n = 5), prolactinoma (n = 8), and FSH producing adenoma (n = 1)), 3) nonfunctioning pituitary adenoma+craniopharyngioma (n = 48, nonfunctioning pituitary adenoma (n = 35) and craniopharyngioma (n = 13)), 4) primary AI (n = 18), and 5) other causes of hypopituitarism (n=22, including congenital hypopituitarism (n = 6), hypopituitarism after radiotherapy/surgery/traumatic brain injury (n = 7), and other causes such as pituitary inflammation or Sheehan's syndrome (n = 9)). $CORT_{hair}$ was lowest in patients with CD, but group differences did not reach statistical significance ($P = .126$) (Figure 1). The self-reported hydrocortisone dose was significantly different between groups ($P = .003$), with patients with primary AI using a higher dose (24.7 ± 4.5 mg) compared

to patients with CD (20.0 ± 4.8), NFA+CP (20.9 ± 3.8) or other causes of hypopituitarism (19.2 ± 5.4).

Table 1. Clinical characteristics of AI patients (males vs. females)

	Patients with AI (n = 120)	Males with AI (n = 46)	Females with AI (n = 74)	P value
Age (years)	55.0 ± 14.7	57.2 ± 14.8	53.6 ± 14.6	.167[b]
BMI (kg/m^2)	28.0 ± 5.1	27.5 ± 3.5	28.3 ± 5.9	.799[b]
Duration of follow-up (years)	18.5 ± 13.3	18.2 ± 12.6	18.7 ± 13.8	.995[b]
Use of external glucocorticoids #	15 (13%)	5 (11%)	10 (14%)	.702[c]
Hair cortisol levels*	23.7 (14.0 – 84.7)	75.3 (26.2 – 150.1)	19.7 (11.6 - 38.5)	**<.001[a]**
Hair cortisol above our lab-internal cut-off (52 pg/mg)	41 (34%)	27 (59%)	14 (19%)	**<.001[c]**
Daily hydrocortisone dose (mg)	21.1 ± 4.5	21.5 ± 5.1	20.8 ± 4.2	.334[b]
Daily hydrocortisone dose (mg/kg)	0.26 ± 0.07	0.2 ± 0.07	0.3 ± 0.07	.065[b]
Daily hydrocortisone dose (mg/BSA)	10.7 ± 2.4	10.3 ± 2.5	11.0 ± 2.3	.077[b]
Hair dyed	44 (37%)	0 (0%)	44 (60%)	**<.001[c]**
Hair bleached	18 (15%)	0 (0%)	18 (24%)	**<.001[c]**
Hair permed	3 (3%)	1 (2%)	2 (3%)	.848[c]
Use of hair product	60 (50%)	17 (37%)	43 (58%)	**.024[c]**
Frequency hair wash > 3 times/week	42 (35%)	21 (46%)	21 (28%)	.061[c]

Data are presented as mean (standard deviation), and as n (valid percentage). a Independent samples t-test, b Mann-Whitney U-test, c Chi-square test. AI, adrenal insufficiency; BMI, body mass index; BSA, body surface area; #: use of other external glucocorticoids (in addition to their regular hydrocortisone substitution). P value: AI males vs. AI females.

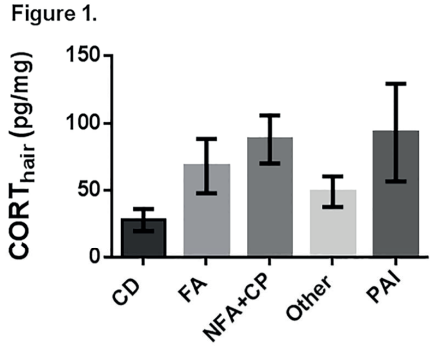

Figure 1. Comparison of CORThair between patient groups.

Mean hair cortisol levels ($CORT_{hair}$) +/- standard error to the mean, stratified per patient category as follows: 1. CD: AI due to previous treatment for Cushing's disease (n = 18); 2. FA: other functioning pituitary adenomas (n = 14, including acromegaly (n = 5), prolactinoma (n = 8), FSH producing adenoma (n = 1)); 3. NFA+CP: non-functioning pituitary adenomas (n = 48, including craniopharyngeoma (n = 13) and NFA (n = 35)); 4. PAI: primary adrenal insufficiency (n = 18); 5. Other: other causes of hypopituitarism (n = 22, including congenital hypopituitarism (n = 6), hypopituitarism after radiotherapy/surgery/traumatic brain injury (n = 7), other causes such as pituitary inflammation or Sheehan's syndrome (n = 9)). The figure shows a difference in $CORT_{hair}$ between patients with AI due to previous treatment for CD and the other groups, but this difference was not found to be statistically significant (P = .126).

QoL

Compared to healthy controls, patients with AI reported worse QoL on all subscales (except general health perception, SF-36) (P < .05). After stratifying for gender, male patients reported worse QoL on 12 of the 15 subscales (P < .05) and female patients reported worse QoL on 14 of the 15 subscales (P < .001) in comparison to controls (Table 2).

Comparing QoL between the different etiology groups revealed significantly more depressive symptoms (HADS) in patients with CD (7.3 ± 4.0) relative to patients with NFA+CP (4.3 ± 3.5) (P = .022) (Figure 2). Furthermore, patients with CD reported more physical fatigue (14.7 ± 2.0), more reduced activity (12.9 ± 1.2) (MFI-20), and worse mental health (58.9 ± 20.2) (SF-36) compared to patients with PAI (11.7 ± 4.7; 10.7 ± 4.2; 77.7 ± 18.2) (P = .004, P = .009, P = .044, respectively). Considering that only patients with CD differed from the other groups, QoL analyses were corrected for etiology of CD.

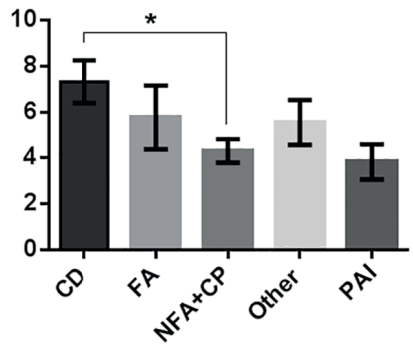

Figure 2. Comparison of depressive symptoms (HADS) between patient groups.
Mean Depressive and Anxiety symptoms as measured by the Hospital Anxiety and Depression Scale (HADS) +/- standard error to the mean, stratified by the following patient categories: 1. CD: AI due to previous treatment for Cushing's disease (n = 18); 2. FA: functioning pituitary adenomas (n = 14, including acromegaly (n = 5), prolactinoma (n = 8), FSH producing adenoma (n = 1)); 3. NFA+CP: non-functioning pituitary adenomas (n=48, including craniopharyngeoma (n = 13) and NFA (n = 35)); 4. PAI: primary adrenal insufficiency (n = 18) 5. Other: other causes of hypopituitarism (n = 22, including congenital hypopituitarism (n = 6), hypopituitarism after radiotherapy/surgery/traumatic brain injury (n = 7), other causes such as pituitary inflammation or Sheehan's syndrome (n = 9).

Relations between $CORT_{hair}$ and QoL (Table 3)

Correlations between $CORT_{hair}$ and QoL, adjusted for age, gender, and etiology CD revealed that in the whole group, higher $CORT_{hair}$ correlated at trend level with more limitations in daily activities (EQ-5D) (r = 0.180, P = .059). After stratification for gender, it was observed that in male patients higher $CORT_{hair}$ was associated with more physical fatigue (r = .355, P = .018). In female patients higher $CORT_{hair}$ was associated with more limitations in daily activities (r = 0.239, P = .046) and more pain (r = 0.269, P = .024) (EQ-5D).

In the whole group, QoL of patients with $CORT_{hair}$ above the lab-internal cut-off for normal was not different from patients with $CORT_{hair}$ in the normal range (P > .05). However, female patients with $CORT_{hair}$ levels above the lab-internal cut-off (n = 14 (19%)) reported lower physical functioning (52.9 ± 28.7, P = .025) and more pain on the SF-36 (52.8 ± 29.7, P = .033), as well as on the EQ-5D (2.2 ± 0.8, P = .049) relative to females with $CORT_{hair}$ within the

Table 2. Quality of life scores in patients with AI vs. healthy controls

		Patients with AI (n=120)	Healthy controls (n=437)	P value[1]	Males with AI (n=46)	Healthy males (n =136)	P value[2]	Females with AI (n=74)	Healthy females (n=301)	P value[3]
SF-36	Physical functioning	73.3±24.7	88.2±16.6	**<.001**	82.6±20.3	90.1±15.9	**.003**	67.4±25.5	87.3±16.9	**<.001**
	Social functioning	67.4±28.8	88.4±18.7	**<.001**	75.3±24.4	91.7±15.4	**<.001**	62.5±30.4	86.9±19.8	**<.001**
	Role limitation (physical)	53.4±44.5	84.5±31.3	**<.001**	66.3±41.2	87.8±26.2	**<.001**	45.4±44.8	83.1±33.0	**<.001**
	Role limitation (emotional)	72.8±40.5	86.5±29.5	**<.001**	82.6±32.0	90.1±24.4	.102	66.7±44.1	84.8±31.4	**<.001**
	Pain	73.0±26.8	85.8±18.5	**<.001**	82.0±21.1	88.0±16.4	.106	67.4±28.5	84.8±19.3	**<.001**
	General health perception	46.8±22.2	71.6±18.7	**<.001**	50.7±22.7	74.5±17.1	**<.001**	44.4±21.7	70.4±19.3	**<.001**
	General perception of change in health	50.3±22.7	53.6±17.9	.140	49.4±18.8	54.4±18.0	.210	50.9±24.9	53.2±17.9	.344
HADS	Anxiety	5.5±3.9	4.1±3.2	**<.001**	3.9±2.7	3.0±2.7	**.036**	6.4±4.2	4.5±3.3	**<.001**
	Depression	5.1±4.1	2.8±2.8	**<.001**	4.2±3.9	2.7±2.5	**.015**	5.6±4.1	2.8±3.0	**<.001**
	Total score	10.5±7.3	6.8±5.3	**<.001**	8.2±6.0	5.7±4.4	**.016**	12.0±7.6	7.3±5.6	**<.001**
MFI-20	General fatigue	11.7±2.2	8.5±4.0	**<.001**	11.0±2.2	7.5±3.5	**<.001**	12.1±2.1	8.9±4.2	**<.001**
	Physical fatigue	13.1±2.6	7.6±3.7	**<.001**	12.3±2.6	7.3±3.5	**<.001**	13.5±2.3	7.7±3.8	**<.001**
	Reduced activity	12.2±2.3	7.2±3.5	**<.001**	11.8±2.5	7.1±3.3	**<.001**	12.4±2.2	7.2±3.5	**<.001**
	Reduced motivation	11.4±2.6	7.3±3.4	**<.001**	11.6±2.9	7.2±3.3	**<.001**	11.3±2.5	7.3±3.4	**<.001**
	Mental fatigue	11.3±2.3	7.8±3.9	**<.001**	10.9±2.2	6.9±3.4	**<.001**	11.5±2.3	8.2±4.0	**<.001**

Mann-Whitney U-test s. Data are presented as mean (standard deviation). AI: adrenal insufficiency. P value[1]: patients with PAI vs. Healthy controls; P value [2]: AI males vs. healthy males; P value[3]: AI females vs. healthy females.

normal range. No differences in QoL were found between male patients with $CORT_{hair}$ above the lab-internal cut-off (n = 27 (59%)), and male patients with $CORT_{hair}$ within the normal range (P > .05). Regression analyses including age, gender, and etiology CD, as well as $CORT_{hair}$ as a quadratic term did not render significant results.

Table 3. Correlations between QoL, $CORT_{hair}$ and hydrocortisone dose

		Patients with AI[a]		Males with AI[b]		Females with AI[b]	
		$CORT_{hair}$	HC dose	$CORT_{hair}$	HC dose	$CORT_{hair}$	HC dose
SF-36	Physical functioning	-.097	-.208*	-.019	-.200	-.122	-.164
	Vitality	-.068	-.251**	.067	-.085	-.164	-.334***
	Change in health	.015	-.317***	.011	-.258	.031	-.349***
MFI-20	Physical fatigue	.120	.136	.335*	.203	-.028	.066
EQ-5D	Activity	.180	.206*	.016	.153	.239*	.264*
	Pain	.131	.134	-.054	.013	.269*	.215
	VAS	-.071	-.297***	.171	-.319*	-.164	-.307*

[a] partial correlations correcting for age and gender; [b] partial correlations correcting for age. *P < .05; **P< .01; *** P< .005. AI: adrenal insufficiency. $CORT_{hair}$ (pg/mg); hydrocortisone dose (mg). Only significant correlations are shown.

Relationships between daily hydrocortisone intake and QoL (Table 3)

Correlations between hydrocortisone intake and QoL, adjusted for age, gender, and etiology CD, revealed that in the whole group, higher hydrocortisone intake was associated with more impairments in physical functioning (r = -0.208, P = .027), less vitality (r = -0.251, P = .007), a greater decrease in perceived health (change in health) (r = -0.317, P = .001) (SF-36), more limitations in daily activities (r = 0.206, P = .032), and a worse perceived health status (r = -0.297, P = .002) (EQ-5D). After stratification for gender, it was observed that higher hydrocortisone intake was associated with a worse perceived health status in male patients (r = -0.319, P = .048). In female patients, higher hydrocortisone intake was associated with less vitality (r = -0.334, P = .005), a greater change in health (r = -0.349, P = .003) (SF-36), more limitations in daily activities (r = 0.264, P = .028), and a worse perceived health status (r = -0.307, P = .012) (EQ-5D). Regression analyses including age, gender, and etiology CD, as well as daily hydrocortisone dose as a quadratic term revealed a significant quadratic contribution of hydrocortisone dose to depressive symptoms (HADS) (β = 1.150, P = .019), mental fatigue (MFI-20) (β = -1.079, P = .033), physical functioning (β = -0.946, P = .046), social functioning (β = -1.232, P = .012), change in health (SF-36) (β = -1.031, P = .039), pain (β = 1.413, P = .004) and perceived health status (EQ-5D) (β = -1.022, P = .036), indicating that relatively low, as well as relatively high hydrocortisone intake was associated with more depressive symptoms, more limitations in physical functioning and social functioning, more pain, and lower perceived health, but less mental fatigue.

Regression analysis including $CORT_{hair}$ and hydrocortisone intake

Regression analysis including both $CORT_{hair}$ and daily hydrocortisone dose, as well as age, gender, and etiology CD, revealed a significant contribution of daily hydrocortisone dose to physical functioning (β = -0.182, P = .046) change in health (SF-36) (β = -0.254, P = .008), limitations in physical activities (β = 0.204, P = .034) perceived health status (EQ-5D) (β = -0.277, P = .004). No significant contribution of $CORT_{hair}$ was found in this by using this regression model. Post-hoc analyses on these significant results using the same regression analyses, but without $CORT_{hair}$, resulted in slightly increased beta's (increases ranging from .008 to .022), indicating that part of the variation of $CORT_{hair}$ was explained by hydrocortisone intake, which is not surprising considering the association between daily hydrocortisone intake and $CORT_{hair}$ (r = 0.185, P = .047).

DISCUSSION

The present exploratory study confirmed that patients with AI report more impairments in QoL compared to healthy controls (2-5), which is dependent on the cause of AI and demonstrated that daily hydrocortisone intake was inversely correlated with QoL (physical aspects). This is in accordance with some (5;13;28), but not all studies (2;4;29). Interestingly, this association was not found with systemic cortisol exposure, since only a few aspects of QoL were associated with $CORT_{hair}$, suggesting that QoL impairments are not per se due to chronic overtreatment with hydrocortisone. Nevertheless, $CORT_{hair}$ did explain a part of the variation of the observed associations between daily hydrocortisone intake and QoL, indicating that the actual cumulative cortisol exposure should also be taken into account.

Previous QoL studies in patients with AI identified several influencing factors, such as autoimmune co-morbidity (30), delay of diagnosis (30), higher age at manifestation, and female gender (30). Furthermore, it is suggested that intrinsic imperfections in replacement therapy also play a role (10). The present study is the first to examine the relation between actual chronic cortisol tissue exposure and QoL in patients with AI as measured by $CORT_{hair}$. Based on this first explorative study it seems that associations between hydrocortisone intake and QoL are not (directly) influenced by cortisol exposure. This suggests that QoL impairments in patients with AI are not per se related to higher cortisol exposure, but it might be more obvious that the relation between hydrocortisone intake and QoL is (at least partly) explained by that patients who take more hydrocortisone basically need more hydrocortisone. Furthermore, assessing the potential effect of occasionally taking higher hydrocortisone doses did not reveal a significant effect (data not shown). Cortisol acts in the central nervous system by binding to mineralocorticoid- and glucocorticoid receptors. The current notion is that the effects of cortisol binding to mineralocorticoid and glucocorticoid receptors follow an inverted u-shaped dose response curve, with both pathological low and high cortisol levels negatively affecting the mediating function of these receptors (31). This mechanism might underlie the

observed impairments in QoL in female patients with $CORT_{hair}$ above the lab-internal cut-off. Since there is no explicit lower limit of $CORT_{hair}$, there is no evidence that underreplacement negatively affects QoL. Interestingly, this inverted u-shaped dose response curve was identified in the quadratic associations found between hydrocortisone intake and physical, mental and social aspects of QoL.

Despite the heterogeneous origin of AI in this cross-sectional analysis, we found that $CORT_{hair}$ correlated with two physical aspects of QoL (physical activities and pain) in female patients, and one physical aspect in male patients (physical fatigue). In addition, female patients with $CORT_{hair}$ above the lab-internal cut-off reported more impairment in QoL relative to females with $CORT_{hair}$ below the lab-internal cut-off. This difference was not found for male patients. The found gender difference in $CORT_{hair}$ in the present sample with males demonstrating higher $CORT_{hair}$ than females, was previously described (17) and may be due to, among other factors, sex-specific differences in levels of circulating cortisol binding globulin. Therefore, analyses of the present study were stratified for gender. Furthermore, in male patients higher $CORT_{hair}$ was associated with higher BMI (17), suggesting a metabolic effect of overexposure. Recently, Quinkler et al. demonstrated in patients with AI using conventional hydrocortisone replacement that switching to once-daily hydrocortisone dual release tablets did not ameliorate QoL, although BMI and HbA1c improved (32). Together with the results of the present study, this would suggest that more adequate cortisol exposure predominantly affect somatic outcome, and to a lesser extent patient-perceived well-being, in particular in males. Furthermore, it was observed that patients with CD showed lower $CORT_{hair}$ relative to the other groups (although not significant). We postulate that this observation is also related to the gender effect since ninety-four percent of the patients with CD were females, and comparing $CORT_{hair}$ between female patients with CD and other female patients revealed no significant results (data not shown). Furthermore, it can be speculated that low $CORT_{hair}$ found in patients with CD might be explained by irreversible changes in cortisol metabolism (e.g. more efficient breakdown of cortisol) related to the previous exposure to elevated cortisol levels.

In addition, the observation that patients with AI due to previous treatment for CD reported more QoL impairments compared to the other diagnostic groups, while also having the lowest $CORT_{hair}$ (not significant), could potentially be explained by the fact that these patients have been exposed to excessive cortisol levels in the past. Previous literature reported that potential damage caused by this excessive exposure to cortisol might only be party reversible (33;34). Therefore, it might be that QoL impairments in the CD group are to a larger extent explained by the previous hypercortisolism, than due to current cortisol levels as measured by $CORT_{hair}$.

As previous studies show, assessment of $CORT_{hair}$ is a useful tool in the diagnosis of Cushing's syndrome and potentially also for AI (16;35) or as indicator of somatic disease and distress (36-38). Furthermore, the assessment of $CORT_{hair}$ in the present study enabled us to

discriminate between cause and consequences, since impairments in QoL were associated with a higher hydrocortisone intake, but were not reflected by higher $CORT_{hair}$. Several small studies on the relation between $CORT_{hair}$ and depressive symptoms, anxiety or general well-being in subjects without AI have been published, however at present no other study primarily focused to this extent on QoL in relation to $CORT_{hair}$ in AI (38-41). Younge and colleagues assessed $CORT_{hair}$, as well as QoL and psychological parameters (i.e., SF-36, HADS) in patients with structural heart disease. They demonstrated that higher $CORT_{hair}$ was correlated with lower self-reported physical functioning, which remained significant after adjustment for age, gender and BMI. No significant correlations were found on other aspects (42). Similarly, in the present study, physical aspects of QoL were associated with hair cortisol levels, while no correlations were found with other aspects of QoL.

In the present study, $CORT_{hair}$ and some physical aspects of QoL were associated with each other in a heterogeneous group of patients with AI. It is important to acknowledge that we studied correlations within a group of patients with AI with impairments in QoL (2-6). This group is potentially yielding a relatively small variation of QoL, thereby impeding finding associations between $CORT_{hair}$ and QoL. Other aspects that should be taken into account while interpreting the results are the multidimensional character of QoL (43), and the possibility that the used generic and domain-specific QoL questionnaires might have been not sensitive enough. Although a disease-specific QoL questionnaire for primary adrenal insufficiency (i.e. AddiQoL (44;45)) could have been more sensitive and suitable, it was not used because it has not yet been translated and validated into the Dutch language. In addition, it should be acknowledged that although the present sample was heterogeneous regarding etiology of AI and that both patients with primary and secondary AI were included, it provides a representative sample of everyday clinical practice. Finally, no conclusions can be drawn about causality due to the cross-sectional design of this study. Future studies using a longitudinal design could provide more information about the time course of QoL impairments, as well as the contribution of $CORT_{hair}$.

In conclusion, this is the first report that further explored the relation between QoL, hydrocortisone intake and actual cortisol exposure in AI patients by measuring hair cortisol, a marker of long-term systemic cortisol exposure. Patients with AI demonstrated several impairments in QoL which were sex-specifically associated with hydrocortisone intake, but were to a lesser extent reflected by chronic cortisol exposure as measured by hair cortisol, suggesting that QoL impairments in patients with AI are not explained by the effect of prolonged exposure to elevated systemic cortisol levels.

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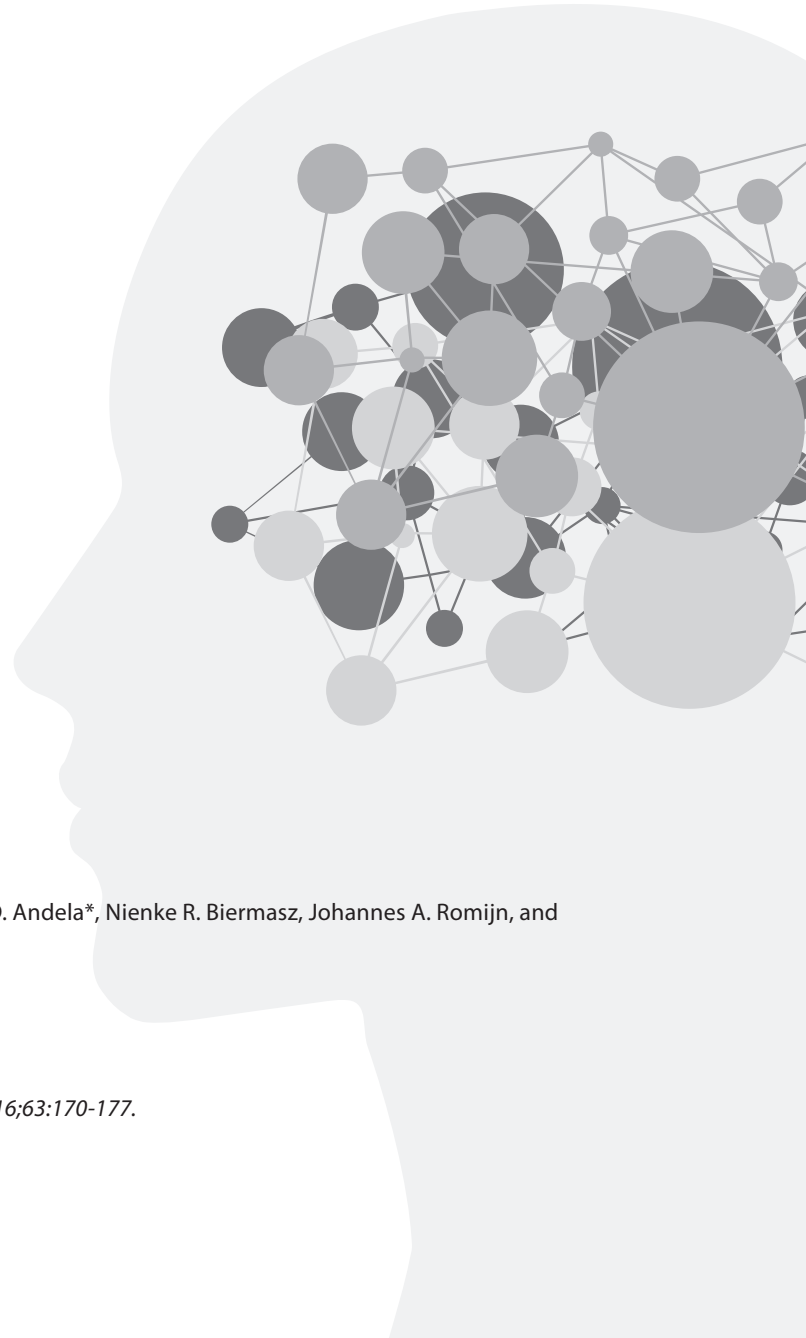
CHAPTER 7

Mild cognitive deficits in patients with primary adrenal insufficiency



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ABSTRACT

Background: The brain is a major target organ for cortisol considering its high density of glucocorticoid receptors. Several states of hypothalamus-pituitary-adrenal dysregulation point towards impairments in cognitive functioning. However, there is a very limited body of research on the effects of hypocortisolism on cognitive functioning.

Aim: To evaluate cognitive functioning in patients with hypocortisolism (i.e. primary adrenal insufficiency (PAI)) and to examine the possible effect of postponing early-morning hydrocortisone intake on cognitive functioning.

Methods: Thirty-one patients with PAI on regular morning hydrocortisone intake and 31 healthy matched controls underwent nine neuropsychological tests evaluating memory and executive functioning. In addition, the effect of normal timing and postponement of morning hydrocortisone intake on neuropsychological tests were assessed in an additional 29 patients with PAI.

Results: Compared to controls, patients with PAI performed worse on auditory and visual memory tasks (all $P \leq .024$) and executive functioning tasks (all $P \leq .012$). In contrast, patients performed better on a concentration and an attention task (both $P < .05$). Postponement of hydrocortisone intake in the morning did not affect the outcomes of neuropsychological tests.

Conclusion: Patients on long-term hydrocortisone replacement for PAI show mild cognitive deficits compared to controls. There was no effect of postponement of regular hydrocortisone intake on cognition.

INTRODUCTION

In the human brain, the effect of cortisol is mediated via two types of receptors: the mineralocorticoid receptors (MRs) and the glucocorticoid receptors (GRs). 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 (1). Activation of the MR leads to retrieval of previously learned tasks and behavioural responses to new situations, while GR activation is responsible for the consolidation of new information (2).

The mediating functions of MR and GR activation regarding behaviour have been studied in animal models. Long-term-potentiation (LTP, reinforcement of synaptic contacts contributing to storage of information) is enhanced when cortisol levels are mildly elevated, resulting in activation of all MRs and some of the GRs. When GRs are extensively activated because of high levels of cortisol, LTP was impaired while long-term-depression (reduction of synaptic contacts causing the opposite effect of LTP) was enhanced (3). In accordance, it has been postulated that cortisol levels follow an inverted u-shaped dose response curve, with very low cortisol levels (predominantly activating the MRs), as well as very high cortisol levels (activating MRs and a large amount of GRs) negatively affecting the mediating function of these receptors on information processing. This work has been elaborated further in humans by Lupien et al. (4), who showed that memory performance can be modulated by pharmacological manipulations of glucocorticoid levels, with too low, as well as too high glucocorticoid levels resulting in impaired memory function.

The negative effects of exposure to cortisol excess on the human brain and cognition have been shown in patients with Cushing's disease (CD). Patients with active CD suffer from hypercortisolism and demonstrate cognitive impairment and abnormal brain characteristics (5-8), which partly persist even after long-term remission (9-12). In contrast to the large amount of data on the effects of hypercortisolism on the human brain and cognitive functioning, limited data are available on cognitive functioning in patients with hypocortisolism (see Table 1 for an overview of studies). Primary adrenal insufficiency (PAI) or Addison's disease is caused by damage to the adrenal gland, most frequently caused by auto-immunity or following bilateral adrenalectomy. As a result, cortisol and aldosterone secretion is reduced dramatically or even completely absent. Patients are treated with hydrocortisone (HC) replacement in order to mimic the circadian rhythm of cortisol secretion as best as possible. However, even on stable treatment for PAI, patients reported impairments in QoL (13-15). Interestingly, Tytherleigh et al. (2004) investigated the role of MR versus GR activation in information processing in nine patients with PAI. In accordance with findings of animal studies, it was demonstrated that in comparison with GR activation only, working memory and episodic declarative memory performance was better when both receptors were activated. This study further supports that balanced activation of both receptor types is necessary for optimal memory functioning

Table 1. Literature overview of studies reporting on cognitive functioning in patients with adrenal insufficiency

	N	Gender M/F	Age yr	Design	Controls	Cognitive measures	Cognitive domains	Outcomes
(16)	9	NA	Mean: 37.9	P	NA	Forward and backward digit span Item recognition HVLT Names Test Doors Test Letter Naming Speed of comprehension Category naming	Working memory Episodic and semantic components of declarative memory	Patients performed better on the digits backward task when GR and MR were activated compared to only GR activation. They performed better on the HVTL when both receptors were activated compared to only MR or GR activation
(17)	14	3/11	Range : 29-70	P	NA	WISC DST LCT VIG STM TMT-A/B	Intellectual functioning Mental flexibility Focused attention Vigilance Short-term memory Executive functioning	Mimicking the physiological rise in cortisol secretion during the night did not affect cognitive functioning compared to cognitive functioning during normal HC intake. A significant negative correlation was found between cortisol levels and short-term memory performance.
(32)	8	2/6	Mean: 52.6 SEM: 3.2	C-S	Gender-, age-, BMI matched healthy controls	Stroop-cwt Word list	Selective attention Short-term memory	Patients performed worse on the word-reading and color-naming subtest (attention).
(31)	27	7/20	Mean: 48.7 SD: 15.36	C-S	Age-, education-, gender-and race matched healthy controls	BTACT	Episodic memory Working memory Executive functioning Reasoning Speed of processing	Patients performed worse onepisodic memory and speed of processing.

(30)	30	9/21	Mean: 52.4 SD: 14.4	C-S	Age-, education-, and gender matched healthy controls	ZVT Stroop-cwt Digit span AVLT ROCF AMT	Executive functioning Concentration Verbal memory Visual memory Working memory Autobiographical memory	Patients performed worse on verbal learning. There were no significant differences in the other domains.
(18)	47	29/18	Mean: 51 SD: 14	Randomized double blind cross-over study	Intervention study: 10 weeks low dose HC (0.2-0.3 mg/kg body weight/day) vs. 10 weeks high dose HC (0.4-0.6 mg/kg body weight/day)	RBMT 15 Words test Digit span RCFT 15 Figures test TAP: vigilance, divided attention, visual scanning, alertness Verbal fluency tests TMT Reading the Mind in the Eyes test	Memory Attention Executive functioning Social cognition	There were no significant differences in cognitive functioning between the low dose and the high dose regimen.
Present study	**60**	**23/37**	**Mean: 49.0 SD: 12.4**	**C-S**	**Age-, gender-, education matched healthy controls** **Patients with PAI who postponed HC intake** **References values of patients with remission of CD**	**WMS RAVLT RCFT FAS TMT-A/B LDST Stroop-cwt SART GIT-2**	**Verbal intelligence Working memory Short-term memory Mental flexibility Verbal fluency Psychomotor speed Speed of processing Executive functioning Sustained attention**	**Patients performed worse on memory and executive functioning tasks, but better on a concentration task and made fewer errors during a focused attention task. No differences were observed compared to patients who postponed HC intake, except for fewer repeats during a verbal fluency task. Patients performed generally similar to patients in remission of CD.**

in humans (16). Furthermore, Harbeck et al. (17) investigated the effects of hydrocortisone infusion during the night on cognitive functioning in patients with PAI, and concluded that higher cortisol levels were associated with worse short-term memory performance. Recently, Werumeus Buning and colleagues (18) explored the effect of low versus high dose HC on cognition in patients with secondary adrenal insufficiency. The researchers found no significant effect on cognition after 10 weeks of treatment with a high dose of HC compared with patients on a lower dose of HC.

The number of studies on cognitive functioning in patients with PAI is limited. Therefore, the aim of the present study was to investigate cognitive functioning, including memory and executive functioning, in patients with PAI on regular morning HC intake. Furthermore, we aimed to investigate the direct effect of very low cortisol levels on cognitive functioning by examining the effect of postponement of HC intake in patients with PAI. We hypothesized that patients with PAI have cognitive impairments, which would be in line with the inverted u-shaped dose response curve of cortisol. Furthermore, we hypothesize that postponement of habitual HC intake will lead to more impaired cognitive functioning.

MATERIAL AND METHODS

Participants

Patients with PAI were recruited via the outpatient clinic of the department Endocrinology at the Leiden University Medical Center (LUMC) and by advertisement via the Dutch Adrenal Patient Society for Addison and Cushing Patients (NVACP; www.nvacp.nl). Thirty-nine patients were derived from the patient network and 21 patients from the LUMC outpatient clinic. A final number of 60 participants were included in the present study (23 men and 37 women, mean age 49.0 ± 12.4 years). Patients were excluded in case of present or previous drug or alcohol abuse, any neurological diagnosis such as CVA, cerebral trauma, or dementia. PAI had been diagnosed based on the classical clinical symptoms and biochemical confirmation of adrenal insufficiency in the presence of increased ACTH concentrations. Adrenal insufficiency was diagnosed when basal early morning cortisol concentrations were below the reference range of normal (<0.12umol/l) or below 500 nmol/l after stimulation with ACTH. Thirty-eight patients (63%) had been diagnosed with PAI due to autoimmune disease with positive autoantibodies against the adrenal cortex, 5 patients (8%) had been diagnosed with PAI due to non-autoimmune causes (e.g. congenital adrenal aplasia, adrenal calcification), and 2 patients (3%) after bilateral adrenalectomy for pheochromocytomas. The origin of PAI was unknown in 15 patients (25%).

All patients were on hydrocortisone replacement with a mean duration of 9.7 ± 8.2 years (range 2-38 years), as prescribed by their individual physicians. Eighty-three percent of the patients also used fludrocortisone in addition to hydrocortisone. Additional medical therapy

included DHEA (23%), levothyroxine for concomitant Hashimoto's disease (43%), anti-hypertensive drugs (12%), and oral contraceptives (8% of the female patients). Forty-one percent of female patients were postmenopausal.

The controls were obtained from online advertisements and advertisements in grocery stores and were matched for gender, age, and education. Exclusion criteria were present or previous drug or alcohol abuse, any neurological diagnosis or endocrine disease. The Medical Ethics Committee of the LUMC approved the protocol and written informed consent was obtained from all subjects.

Study procedure

All patients were invited to the LUMC for the neuropsychological examination. Patients were randomly assigned to condition 1: taking their regular morning HC dosage on the day of the neuropsychological assessment, or condition 2: postponing their regular morning HC dosage on the day of the neuropsychological assessment. All patients were instructed to rise, take their HC substitution (condition 1), and eat a standardized breakfast between 6 and 7 a.m. Both patients and controls were asked to take a standardized breakfast, which consisted of a cup of tea without sugar, and one slice of bread. Before the neuropsychological evaluation started, blood pressure, heart rate, and glucose levels were measured. The neuropsychological examination started at 9.00 a.m. and took approximately 90 minutes. Patients in condition 2 who postponed their regular morning HC intake were asked to take their medication in the presence of the examiner directly after the neuropsychological evaluation.

Cognitive evaluation

In order to assess cognitive functioning, nine neuropsychological tests were completed. A functional classification was used to subdivide the tests into the cognitive domains memory and executive functioning (19). Since psychopathology can have an effect on cognitive functioning, independent variables related to psychopathology affecting cognitive functioning in patients were explored. The scores on various psychopathology questionnaires (Apathy Scale, Irritability Scale, Mood and Anxiety Symptoms Questionnaire short-form (MASQ), and Hospital Anxiety and Depression Scale (HADS)) were derived from an early study by our research group (15).

Memory

Wechsler Memory Scale (WMS) provides a memory quotient (MQ) based on various subscales (i.e. Information, Orientation, Concentration, Logical Memory, Digit Span, and Visual Memory). A higher MQ indicates a better performance. A MQ between 95 and 104 is considered average (20).

Verbal Learning Test of Rey consists of a list of 15 words, which are visually presented and have to be remembered by the patient. There is a three-trial presentation of this list. After

each trial, the patient is asked to recall the remembered words. Furthermore, there is a fourth delayed reproduction. The amount of recalled words after each trial is counted. The more produced words each trial, the better the learning capability (21). In the present study, only trial 1 (imprinting), trial 2 (immediate reproduction), and trial 4 (delayed reproduction) were used, while trial 3 (second round of immediate reproduction) was omitted from the analyses.

Rey Complex Figure Test measures visual memory. The participant is asked to draw a copy of a complex figure. After three minutes, the patient is asked to draw the complex figure from memory (immediate recall). After 30 minutes, the patient is asked to draw the complex figure again (delayed recall). A higher score indicates better visual memory (22).

Executive functioning

Verbal Fluency Test (FAS) measures verbal fluency and mental flexibility. The participant is asked to produce as many words starting with F, A, or S as possible in one minute. The total amount of produced words is counted, as well as the number of errors and repeats. The more correct words produced, the better the verbal mental flexibility and fluency (23).

Letter-Digit Substitution Test measures mental flexibility, psychomotor speed and speed of information processing. Number of correctly substituted letters and errors within 60 seconds are counted (24).

Stroop color-word test (Stroop-cwt) measures interference sensibility. Patients are asked to name the color of the ink and inhibit reading the word (25).The number of correct and false responses, in 45 seconds, are counted.

Trail Making Test (TMT) requires complex visual scanning and measures motor speed and attention. In part A, the patient is asked to connect the numbers 1 to 15 (TMT-A). In part B, the patient is asked to connect alternately a number and a letter in the right sequence (TMT-B). The time used and the number of errors made are counted. The more time used and the more errors made, the lower the performance on this test (26).

Sustained Attention to Response Task (SART) assesses sustained attention via a go-no-go signal detection task. The participant is subjected to a white digit (1 to 9) 225 times on a black computer screen. Each number is shown 25 times in a predetermined and quasi-random order. Each number is presented for 250 ms, followed by a black screen for 900 ms. Participants are asked to respond to the appearance of each number by pressing a button, except for the number 3. The SART was performed two times, the time in between was spent on other neuropsychological tests (i.e. RCFT, FAS, LDST, Stroop). The average score of the two sessions was calculated and consists of the number of times the button was pressed when a '3' was shown (errors of commission), plus the number of omissions (errors of omission). The reaction time is the average time in milliseconds between the appearance of any number and the subject's presses (27).

Verbal intelligence

The Groninger Intelligence Test 2 (GIT-2) consists of 9 subscales and provides an IQ score. In the present study, only the synonyms subtest was used in order to estimate verbal intelligence. This subtest consists of 20 words. The patient is asked to choose the synonym of each word out of a list of four words. Based on the number of correct answers, an index score can be determined. A higher index score demonstrates a better performance (28).

Cortisol levels

Saliva samples were collected to assess cortisol levels before and after the cognitive tests. Samples were collected using a Salivette® (Sarstedt) containing a sterile polyester swab. The salivettes were used in accordance with the instructions from the manufacturer. All salivettes were centrifuged at 2000*g* for 10 minutes, and filtrates were stored at -20°C until analysis. All samples were analyzed on the same day, using Roche cortisol assays (i.e. competitive electrochemiluminescence immunoassays). The protocol for analyzing salivary cortisol using Roche cortisol assays is described in detail elsewhere (29).

Statistical analyses

All data were analysed using PASW Statistics for Windows version 20.0 (SPSS Inc., Chicago, IL). The primary analysis comprised the comparison of the neuropsychological tests scores of the patients with PAI with regular morning HC intake and the scores of matched healthy controls, by using a linear mixed model with the matched patient-control couples as a random factor. The secondary analysis comprised the comparison of the neuropsychological test scores of patients with regular morning HC intake and patients with postponed intake. In order to compare these scores, an independent-samples t-test was used. When data was not normally distributed, the non-parametric Mann-Whitney Test was used. Since psychopathology can have an effect on cognitive functioning, independent variables related to psychopathology affecting cognitive functioning in patients were explored by linear regression analysis. The standardized β-coefficients of this analysis were reported. To check the appropriateness of assumptions for each statistical analysis Levene's test, Durbin-Watson test, histograms and scatter plots were used. Due to the exploratory nature, the level of significance was set at $P \leq .05$.

RESULTS

Clinical characteristics (Table 2)

A total of sixty patients with PAI were included in the present study, of whom 31 patients with regular morning HC intake at the time of awaking (11 males, 36%), and 29 patients with postponed HC intake until after the tests, which started at 09.00 a.m. (12 males, 41%). In

addition, thirty-one healthy controls were included matched for age, gender, and education to the patients with regular HC intake. Since they were perfectly matched, the 31 patients with regular HC intake did not differ from the 31 matched controls regarding age, gender and education. The clinical characteristics of the patients with regular morning HC intake (n=31) also did not differ from the patients with postponed intake (n=29). The mean weight adjusted dose of HC was 0.31 mg/kg for the entire sample of patients. The mean HC dose per

Table 2. Clinical characteristics of PAI patients with and without HC intake and healthy matched controls

	PAI patients with HC intake (n=31)	**Healthy matched controls (n=31)**	**PAI patients with postponed HC intake (n=29)**	**Test statistic and P-value HC intake versus postponed intake**	**Cohen's *d* effect size HC intake vs postponed intake**
Gender (m/f)	11/20	11/20	12/17	χ^2=0.220, p =0.639	0.121
Age (yrs)	49 (11)	45 (12)	50 (14)	t(58)=0.320, p=0.750	0.083
Educational level					
Low	4 (13%)	4 (13%)	7 (24%)	χ^2=3.998, p=0.135	0.534
Medium	15 (48%)	15 (48%)	7 (24%)		
High	12 (39%)	12 (39%)	15 (52%)		
BMI	27.6 (6.2)	25.3 (3.1)	24.8 (3.8)	U=346.0, p=0.126	0.540
Glucose level	6 (1)	6 (1)	5 (1)	U=371.5, p=0.248	0.402
Blood pressure (systolic, mmHg)	127 (16)	131 (20)	124 (17)	U=358.0, p=0.173	0.182
Blood pressure (dystolic, mmHg)	80 (9)	78 (10)	78 (11)	U=405.0, p=0.505	0.200
Heart rate (bpm)	67 (10)	70 (10)	67 (11)	U=427.5, p=0.742	0.084
Cortisol level before assessment (nmol/L)	20 (14)	NA	4 (2)	U=36.0, p<0.001	1.634
Cortisol level after assessment (nmol/L)	9 (5)	NA	4 (2)	U=79.0, p<0.001	1.554
PAI diagnose (n)					
Autoimmune	19 (61%)	NA	19 (66%)	χ^2=0.178, p=0.915	0.109
Non-autoimmune	2 (7%)	NA	3 (10%)		
BA	1 (3%)	NA	1 (3%)		
Duration of follow-up (yrs)	10 (8)	NA	10 (8)	U=146.5, p=0.855	0.035
Hydrocortisone dose (mg)#	23 (7)	NA	26 (8)	U=492.5, p=0.369	0.285
Fludrocortisone, n (%)	27 (87%)	NA	23 (79%)	χ^2=1.366, p=0.505	0.305
DHEA, n (%)	5 (16%)	NA	9 (31%)	χ^2=1.861, p=0.173	0.358
L-thyroxine, n (%)	13 (42%)	1 (3%)	13 (45%)	χ^2=0.051, p=0.821	0.058
Anti-hypertensive drugs, n (%)	5 (16%)	6 (19%)	2 (7%)	χ^2=1.239, p=0.266	0.290
Insulin, n (%)	0 (0%)	0 (0%)	0 (%)	Constant, p=1.000	NA

Data are mean (SD) or number and %; BA: Bilateral adrenalectomy; # total dose per day.

body surface was 12.20 mg/m2. For the HC intake group, the mean weight adjusted dose of HC was 0.28 mg/kg, while the postponed intake group had a mean weight adjusted dose of HC of 0.34 mg/kg. In addition, the mean HC dose per body surface was 11.4 mg/m2 for the HC intake group, and 13.3 mg/m2 for the postponed intake group. Before testing started at 9 am, the mean salivary cortisol level of the regular HC intake group was 20.4±14.1 nmol/L, while the group that postponed HC intake showed a mean salivary cortisol level of 3.9±2.3 nmol/L. There was a significant difference in cortisol levels between both groups (U=36, P<0.001). After the neuropsychological assessment (at approximately 10.30 am), the mean salivary cortisol level of the HC group was 9.5±5.0 nmol/L, while the group that postponed HC intake showed a mean salivary cortisol level of 3.5±2.1 nmol/L. Again, there was a significant difference in post-test cortisol levels between the groups (U=79, P<0.001).

We asked all participants whether they experienced cognitive limitations. Fifty-seven percent of the patients reported difficulties with attention, compared to 19% of the controls. Seventy percent of the patients reported difficulties with memory compared to 26% of the controls. Problems with executive functioning were reported in 25% of the patients compared to 3% of the controls.

Cognitive functioning of patients with PAI vs. matched healthy controls (Table 3)

Patients with PAI (with regular HC intake, n=31) performed worse on Logical memory (WMS) (P = .006), and recalled fewer words on the Rey Auditory Verbal Learning Test on imprinting (P = .024), immediate recall (P = .001) and delayed recall (P = .016) than their matched controls. On the Rey Complex Figure Test, patients performed worse on the immediate (P = .009), as well as the delayed recall (P = .007). Furthermore, patients had more repeats on the FAS (P = .003) and they needed more time to complete the TMT-B (P = .012) compared with controls. Nevertheless, patients seemed to perform better on the Concentration subscale of the WMS (P = .015) and made fewer errors during TMT-A (P = .041) than controls.

Table 3. Cognitive functioning of patients with PAI vs. Healthy matched controls

		Patients with PAI n=31	Healthy matched controls n=31	Test statistic and P-value	Cohen's *d* effect size
Memory					
Wechsler Memory Scale	Memory Quotient	110.9 (13.7)	113.7 (13.9)	F=0.748, p=0.394	0.223
	Information	5.9 (0.4)	6.0 (0.2)	F=0.682, p=0.412	0.213
	Orientation	5.0 (0.2)	5.0 (0.0)	F=1.000, p=0.325	0.258
	Concentration	7.9 (1.2)	7.1 (1.4)	**F=6.255, p=0.015**	**0.646**
	Logical memory	6.4 (2.3)	8.1 (2.4)	**F=8.749, p=0.006**	**0.764**
	Digit span	10.0 (1.8)	9.9 (1.2)	F=0.007, p=0.934	0.022
	Visual memory	10.2 (2.7)	11.1 (3.6)	F=1.542, p=0.224	0.321

Table 3. Cognitive functioning of patients with PAI vs. Healthy matched controls (continued)

		Patients with PAI n=31	Healthy matched controls n=31	Test statistic and P-value	Cohen's *d* effect size
	Associative learning	16.1 (2.8)	17.0 (3.1)	F=2.566, p=0.120	0.414
Verbal Learning Test of Rey	Imprinting, total	5.3 (1.7)	6.5 (2.5)	**F=5.645, p=0.024**	**0.613**
	Immediate, total	7.9 (1.8)	9.7 (2.5)	**F=12.921, p=0.001**	**0.928**
	Delayed, total	7.5 (2.6)	9.2 (3.4)	**F=6.466, p=0.016**	**0.657**
Rey Complex Figure test	Immediate	18.7 (6.5)	22.2 (7.7)	**F=7.816, p=0.009**	**0.722**
	Delayed	18.6 (6.9)	22.8 (7.8)	**F=8.581, p=0.007**	**0.756**
Executive function					
Verbal Fluency Test (FAS)	# correct	33.6 (12.8)	33.3 (12.9)	F=0.008, p=0.931	0.023
	% repeats	1.1 (1.2)	0.4 (0.6)	**F=10.680, p=0.003**	**0.844**
	% errors	0.9 (1.4)	0.4 (0.7)	F=3.163, p=0.080	0.459
Trail Making Test	Trail A, time	0.3 (0.1)	0.3 (0.2)	F=1.456, p=0.237	0.312
	Trail A, errors	0.1 (0.3)	0.2 (0.4)	**F=4.564, p=0.041**	**0.552**
	Trail B , time	0.9 (0.4)	0.7 (0.4)	**F=7.081, p=0.012**	**0.687**
	Trail B, errors	0.3 (0.7)	0.2 (0.5)	F=1.198, p=0.282	0.283
Letter-Digit Substitution Test	# correct	35.8 (5.1)	37.8 (9.1)	F=1.335, p=0.257	0.298
	# errors	0.2 (0.8)	0.03 (0.2)	F=1.895, p=0.174	0.355
Stroop Color-Word Test	Interference, total	43.5 (7.7)	42.0 (8.2)	F=0.672, p=0.419	0.212
	Interference, mistakes	0.5 (1.9)	0.03 (0.2)	F=1.811, p=0.183	0.347
SART session 1	Errors of ommission	2.52 (6.1)	2.35 (4.9)	F=0.025, p=0.877	0.041
	Errors of commission	9.23 (3.9)	8.9 (4.7)	F=0.104, p=0.749	0.083
	Total error score	11.74 (8.8)	11.26 (8.9)	F=0.079, p=0.781	0.073
	Mean reaction time	309.86 (48.5)	307.03 (51.6)	F=0.055, p=0.817	0.061
SART session 2	Errors of ommission	2.55 (5.5)	1.74 (3.3)	F=1.524, p=0.227	0.319
	Errors of commission	8.74 (4.8)	9.32 (4.9)	F=0.296, p=0.590	0.140
	Total error score	11.29 (8.7)	11.06 (7.1)	F=0.027, p=0.871	0.042
	Mean reaction time	322.73 (73.1)	304.54 (62.6)	F=1.220, p=0.278	0.285
Synonyms subtest of the Groninger Intelligence test	Synonyms score	4.9 (1.5)	4.9 (2.0)	F=0.006, p=0.941	0.020

Data are mean (SD), significant test results are printed bold, intermediate (d=0.5-0.7) and large (d≥0.8) effect sizes are printed bold.

Cognitive functioning of patients with postponed HC intake vs. patients with HC intake immediately after awakening

Patients who postponed their HC intake made fewer repeats (FAS) compared to patients with normal HC intake (P = .025). There were no significant differences on other cognitive tests.

Cognitive limitations and current psychological state in patients with PAI

When combining both patients groups, patients who reported memory impairments scored significantly lower on associative learning (U=248, P=0.046), and were able to recall less words on the immediate recall trial of the Verbal Learning Test of Rey (U=237.5, P=0.028). Furthermore, patients who reported impairments in executive functioning needed more time to finish Trail A of the Trail Making Test (t(57)=-2.211, P=0.031) compared with patients who did not report impairments in executive functioning. There were no differences on tests assessing concentration or attention between patients who reported impairments in those domains and patients who did not.

The possible influence of psychopathology on cognitive functioning was explored by taking both patient groups together. In the memory domain, visual memory was negatively associated with the lack of positive affect subscale of the MASQ (β=-0.578, P=0.006). In the executive functioning domain, the total score on the Stroop Color-Word Test was negatively associated with the lack of positive affect subscale of the MASQ (β=-0.439, P=0.034). The number of errors on trail A of the Trail Making Test was negatively associated with the anxiety subscale of the HADS (β=-0.616, P=0.012) and positively associated with the Irritability scale (β=0.576, P=0.004). On the second session of the SART, the errors of omission was negatively associated with the lack of positive affect subscale of the MASQ (β=-0.578, P=0.006). The mean reaction time on the second session of the SART was positively associated with the depression subscale of the HADS (β=0.767, P=0.004), and negatively associated with the negative affect subscale of the MASQ (β=-0.548, P=0.035). The total error score on the second session of the SART was negatively associated with the lack of positive affect subscale of the MASQ (β=-0.488, P=0.022).

DISCUSSION

The present study demonstrates that patients on HC replacement for PAI performed worse on memory and to a lesser degree on executive functioning tasks when compared with healthy matched controls. It is important to note that patients with PAI in the current study were treated with HC replacement. Nevertheless, they showed subtle cognitive impairments in comparison with healthy matched controls. When patients with regular morning HC intake and patients with postponed HC intake were compared, no immediate deterioration in cognitive functioning was observed (except for one executive functioning task). Furthermore, there were some associations between cognition and patients' current psychological state. Visual memory and various executive functions were related to psychopathology, where a worse score on the cognitive tests was associated with a higher (i.e. worse) score on psychopathology measures.

Although visual memory and executive functioning have been studied in patients with PAI, the observed alterations in visual memory and executive functioning in patients on

long-term HC replacement for PAI have not previously been reported. The other observations in the present study were in accordance with recent other studies, documenting deficits in episodic and verbal memory in patients with PAI (30;31), as well as reduced speed of processing and subtle impairments in attention (31;32). The subtle cognitive impairments observed in patients with PAI might be explained by the HPA-axis dysregulation associated with HC therapy in the presence of primary hypocortisolism. As a result, MR and GR activation may not be optimally adjusted to the situation and the mediating function on memory may not be appropriate (3). This is also in accordance with the study of Tytherleigh et al. (2004), which suggested that a balanced activation of both receptors is needed for optimal memory function in humans (16). It should be noted that the neuropsychological assessment in the present study was performed at 9 am, since longer withdrawal of HC is not indicated for safety reasons. However, cortisol levels are naturally higher in the morning (33) in the healthy population. These higher cortisol level could have negatively influenced cognitive functioning in the healthy controls (34), leading to smaller differences between patients and controls.

In the present study, we did not observe major differences in cognitive functioning between patients with postponed HC intake and patients with regular HC intake. This might be explained by the inverted u-shaped dose response curve with very low cortisol levels (predominantly activating the MRs), as well as very high cortisol levels (activating MRs and GRs both to a large amount) negatively influencing the mediating function of MRs/GRs on information processing (3). It might be that patients were on either end of the inverted u-shape (postponed: only MR activation vs. normal intake: both MR and GR highly activated) and therefore did not differ on cognitive functioning. In addition to dysregulation of HPA-axis within the CNS, another explanation for the results in the present study might be previous long-term hypocortisolism. The effect of prolonged hypocortisolism has been studied in animal models. After adrenalectomy, rats demonstrated neurodegeneration and loss of synaptic function in the hippocampus (2). However, it might also be possible that patients with PAI are exposed to prolonged exposure to elevated cortisol levels, as a result of the imperfect replacement with HC. The suggestion of over-replacement of HC in patients with adrenal insufficiency is supported by a recent study examining hair cortisol levels in patients with adrenal insufficiency on long-term HC replacement. That study showed significantly higher hair cortisol levels in patients with adrenal insufficiency on HC replacement, compared to patients with pituitary deficiencies without adrenal insufficiency and healthy controls (35). The negative effect of exposure to elevated cortisol levels on cognitive functioning and brain characteristics has been reported in patients with CD (5-8). In line with these observations, a direct comparison of the cognitive performance of patients with PAI in the present study, with cognitive functioning of patients in long-term remission of CD (data derived from a previous study by our research group (10)) revealed that patients with PAI and patients in long-term remission of CD perform generally similar (data not shown).

In the review process of the manuscript, there was concern with respect to the presentation of the data without adjustments for multiple comparisons. Simply defined, these adjustments test for no effects in all the primary end points undertaken vs. an effect in one or more of those end points. This is a difficult methodological issue because there are divergent views on the need for statistical adjustment for multiplicity. This is also reflected in the Lancet papers by Schulz and Grimes (36;37), who advocate a restrictive approach toward adjustments for multiple comparisons. If we consider our own data and if we would assume that the differences would mostly reflect false-positive results, it is to be expected that the positive significant results would have been randomly distributed among the different variables. However, this is not the case, as shown in Table 3. We designed this study in our patients with PAI with the primary aim to evaluate cognitive function in detail, in view of the documented abnormalities in previous studies and those observed in experimental animal studies. Indeed, the main results of our study point toward similar adverse effects of PAI documented in previous studies, although these had a different study design. According to Schulz and Grimes, statistical adjustments somewhat rescue the positive results of scattershot analyses. However, we performed a targeted evaluation and analysis focused on cognitive function related to PAI rather than a scattershot analysis of cognitive functions in general. Therefore, in our opinion, our data should not be neglected merely because of the absence of adjustments for multiple comparisons. Moreover, this would carry the serious risk of missing an important association between PAI and cognitive impairments.

Cognitive functioning can be affected by many factors. In order to minimize the effect of external variables, participants and healthy controls were matched for age, gender, and education. However, the present study still has some limitations. Certain prescribed drugs, such as DHEA or levothyroxin, might have an effect on cognitive functioning. Due to power limitations, subgroup analyses to explore possible confounding effects could not be carried out. Future studies might take this into account and explore the effect of DHEA and levothyroxin intake on cognitive functioning in patients with PAI. Another limitation of the present study concerns the different types of PAI. We have no information about the different types of autoimmune causes of PAI, which could be accompanied by comorbidities. These comorbidities in turn could have an effect on cognitive functioning. In addition, regularity of HC intake was not asked nor controlled for. Furthermore, the study was not blinded, and therefore patients were aware of postponed HC intake. This awareness might have resulted in a higher motivation and, therefore, better performance in a subset of the cognitive tests in patients who postponed HC intake compared with patients who took the morning dose of HC at the habitual time. Likewise, patients might have been more motivated than healthy controls, which could explain why patients with HC intake performed better on the concentration subscale of the WMS and made fewer errors during the first trail of the trail making test. Lastly, due to the cross-sectional design of the present study, no causal conclusions could be drawn. Future studies might want to implement a randomized controlled trial with

cross-over design with different substitution dosing regimens. Such a design would provide more relevant data to control our hypothesis that patients' substitution therapy is not equal to physiologic cortisol secretion which in turn might affect cognitive functioning. To provide more insight into the underlying neuronal mechanisms of the observed cognitive deficits in patients with PAI, future (functional) magnetic resonance imaging studies using a longitudinal design are needed.

In conclusion, the present study shows that patients with PAI show mild cognitive deficits compared to controls. Furthermore, the present study is the first to examine the effect of postponing HC intake in patients with PAI and demonstrates that there was no immediate effect of postponement of hydrocortisone intake on cognition. Future studies in animal models and (functional) MRI research in patients with PAI could provide more insight into underlying mechanisms of cognitive impairment due to cortisol imbalances.

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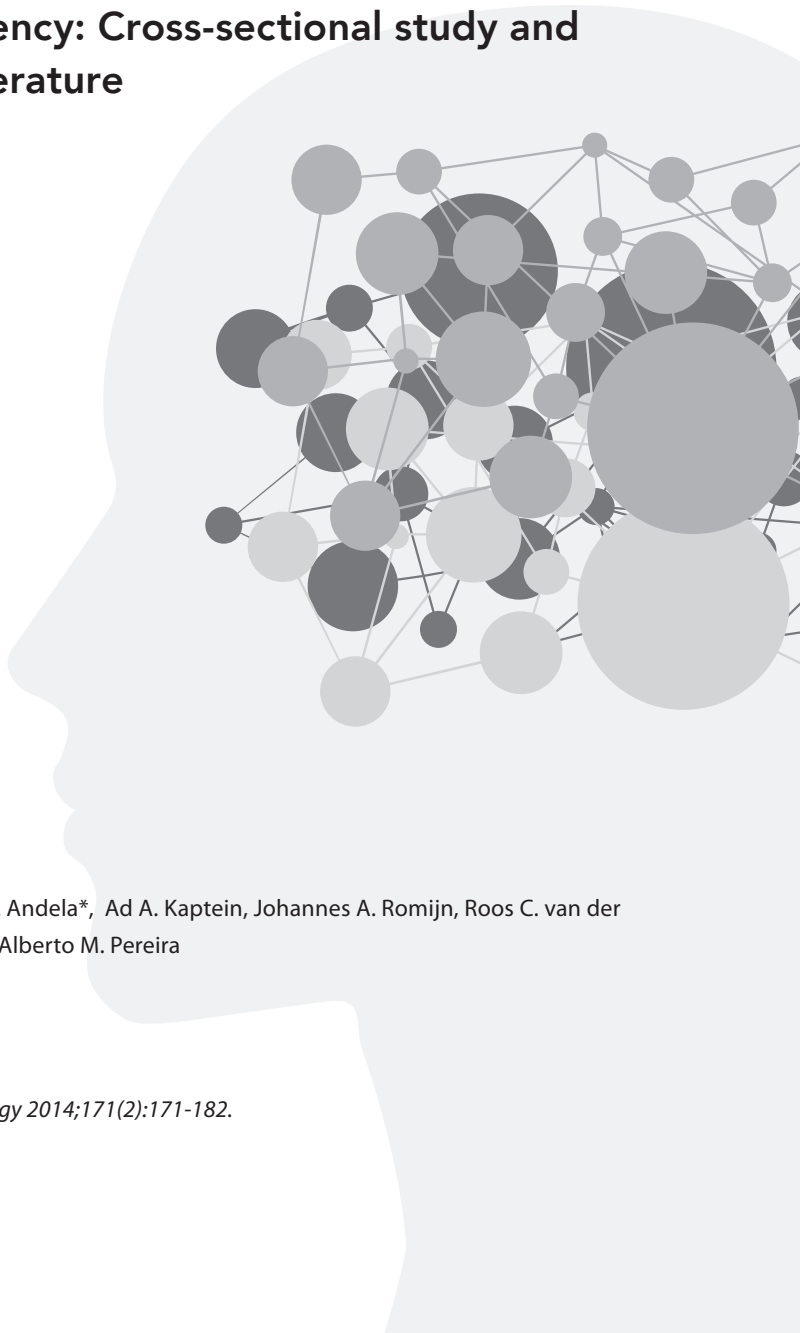
CHAPTER 8

Psychological morbidity and impaired quality of life in patients with stable treatment for primary adrenal insufficiency: Cross-sectional study and review of the literature



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ABSTRACT

Context: A high prevalence of psychological morbidity and maladaptive personality as well as impaired quality of life (QoL) is observed in patients with and without hydrocortisone dependency following (cured) Cushing's syndrome. However, it is currently unclear whether a similar pattern is present in patients with chronic glucocorticoid replacement for primary adrenal insufficiency (PAI).

Objective: To evaluate psychological functioning, personality traits, and QoL in patients with PAI.

Design and subjects: A cross-sectional study including 54 patients with stable treatment for PAI and 54 healthy matched controls. Both patients and controls completed questionnaires on psychological functioning (Apathy Scale, Irritability Scale, Mood and Anxiety Symptoms Questionnaire short-form, and Hospital Anxiety and Depression Scale), personality traits (Dimensional Assessment of Personality Pathology short-form), and QoL (Multidimensional Fatigue Inventory, Short-Form 36, EuroQoL-5D, Nottingham Health Profile, and Physical Symptom Checklist).

Results: Patients with PAI suffered from more psychological morbidity (i.e. irritability and somatic arousal) and QoL impairments compared with controls (all $P<0.01$). There were no differences regarding maladaptive personality traits between patients and controls. However, there was a strong and consistent positive association between the daily hydrocortisone dose and prevalence of maladaptive personality traits (i.e. identity problems, cognitive distortion, compulsivity, restricted expression, callousness, oppositionality, rejection, conduct problems, social avoidance, narcissism, and insecure attachment, all $P<0.05$). There was also a strong relation between the mean daily hydrocortisone dose and both psychological morbidity (i.e. depression, $P<0.05$) and QoL impairments (i.e. general health perception, several measures of physical functioning, and vitality, all $P<0.05$).

Conclusion: Patients with stable glucocorticoid replacement therapy for PAI report psychological morbidity and impaired QoL. Psychological morbidity, impaired QoL, and maladaptive personality traits were all associated with higher hydrocortisone dosages.

INTRODUCTION

Primary adrenal insufficiency (PAI) is characterized by insufficient secretion of glucocorticoids and mineralocorticoids, most frequently caused by autoimmunity or following bilateral adrenalectomy. Replacement therapy consists of hydrocortisone, fludrocortisone, and sometimes, additional DHEA replacement.

Cortisol has a crucial function in the central nervous system via stimulation of both the mineralocorticoid- (MRs) and glucocorticoid receptors (GRs). An appropriate balance between the activation of these two receptors is necessary for adequate stress responses, including behavioral adaptations. Imbalance between MR and GR activations might enhance vulnerability to disease in predisposed individuals. The current notion is that the effects of glucocorticoids binding to MR and GR include an inverted u-shape dose-response curve, indicating that both pathologically low and high cortisol levels negatively affect the mediating functions of these receptors as is the absence of physiological circadian pulsatile secretion (1). The negative influence of glucocorticoid excess on psychological functioning in humans is clearly evident during active Cushing's disease since serious co-morbid psychopathology, such as major depression and anxiety is prevalent (2). Although these symptoms improve substantially after correction of cortisol excess, consistent residual impairments persist, even after prolonged cure of cortisol excess. This is reflected by an increased prevalence of psychopathology and maladaptive personality traits as well as impairments in quality of life (QoL) (3–7) in many patients, either hydrocortisone dependent or independent.

Conversely, it is possible that previous exposure to insufficient glucocorticoid levels and current imperfections in replacement therapy in mimicking the pulsatile secretion of cortisol, such as in PAI, may also be associated with persistent psychosocial effects, considering the inverted u-shape of optimal corticosteroid receptor function. However, in contrast to the large number of reports in patients with Cushing's syndrome, less is known about the effects of previous insufficient cortisol exposure on psychological functioning and QoL in PAI (see Table 1 for an overview). Heijmans and de Ridder (1998) reported a significant relation between personality-related variables (i.e. optimism/pessimism, locus of control) and illness perceptions (8). However, there are no studies on personality traits in patients with PAI. To date, studies in patients with PAI have demonstrated impaired QoL (9–15), and a higher risk for the development of affective disorders such as depression or bipolar disorder (16). The QoL impairments in patients with PAI have been attributed, at least in part, to intrinsic imperfections of hormone replacement therapy (12). In accordance, some studies demonstrated a positive effect of DHEA replacement on QoL (13,17–19). On the other hand, strategies aiming at adjusting cortisol replacement therapy mimicking a more diurnal profile by adjusting the time and frequency of hydrocortisone intake did not positively affect QoL (9,11,20). Furthermore, dosages above 30 mg hydrocortisone per day were associated with worse subjective health status (11).

Table 1. Literature overview of studies reporting on psychological functioning, personality, and QoL, in patients with PAI

Author, year	N	Gender M/F	Age yr	Design	Controls	Domains	Outcomes
Groves, 1988 (49)	7	3/4	*(range)* (22-65)	Prospective	NA	1	Cortisol levels positivity correlated with well-being.
Riedel, 1993 (39)	14	8/6	*(range)* (32-68)	Randomized double-blind cross-over	Normative data	1	At baseline patients scored worse on physical symptoms, mood, psychological activity compared to controles. QoL was influenced by the HC intake scheme, favoring a twice daily instead of a once daily regimen.
Heijmans, 1998a† (8)	110	47/63	*Mean±sd* 41.9±10.6	Observational Cross-sectional	Patients with CFS	1,5,6	Patients with AD reported a different structure of illness perceptions compared to patients with CFS.
Heijmans, 1998b† (50)	110	47/63	*Mean±sd* 41.9±10.6	Observational Cross-sectional	Patients with CFS	4,5	Patients with AD reported different illness perceptions compared to patients with CFS. Disease related and personal variables were associated with illness perceptions.
Heijmans, 1999† (51)	110	47/63	*Mean±sd* 41.9±10.6	Observational	NA	1,5,6	Illness perceptions seemed to play an important role in physical and psychological functioning.
Arlt, 1999, 2000* (17,18)	24	0/24	*Mean±sd* 42 ± 9	Randomized double-blind placebo controlled	NA	1,2	Treatment with DHEA, resulted in improvement in well-being and sexuality in female patients, but at the end of the study there were no differences between placebo and DHEA.
Hunt, 2000 (19)	39	15/24	*Mnd (range)* 40 (25-69)	Randomized double-blind placebo controlled Cross-sectional	Reference data from controls matched by age and sex	1,2	There were no differences between patients at baseline and controls. DHEA replacement improved some aspects of psychological function (self-esteem, mood) and fatigue.
Lovas, 2002 (36)	33	19/14	*Mean±sd* Men: 43.4±6.55 Women: 51.0±5.44	Observational	Normative data	1	Patients demonstrated reduced GHP and vitality, and increased fatigue. Female patients reported reduced physical function.

Table 1. Literature overview of studies reporting on psychological functioning, personality, and QoL, in patients with PAI (continued)

Author, year	N	Gender M/F	Age yr	Design	Controls	Domains	Outcomes
Alonso, 2004 (9)	12	5/7	*Range* 24-75	Cross-sectional	Healthy controls Reference values from general population	1	Patients on a 10-5-5 regimen scored worse on a unit designed questionnaire compared with controls. Compared with the general population, patients had worse QoL, regardless of HC regimen. In addition, total QoL score was worse in patients on a 10-5-5 mg regimen, but there were no differences when patients were on a 20-0-10 mg regimen.
Libe[a], 2004 (52)	20	13/7	*Mean±sd* Men:45±4.4 Women: 45.8±2.6	Randomized placebo controlled	NA	1	DHEA administration did not cause any relevant variation in SHS.
Thomsen[a], 2006 (16)	989	357/632	*Mnd* 51.4	Retrospective Cross-sectional	Patients with osteoarthritis	2	Patients had a 2.68 times greater rate of affective disorders and a 2.12 times greater rate of depressive disorder compared with patients with osteoarthritis.
Hahner[a], 2007 (14)	210	53/157	*Mnd (range)* PAI: M 41.5 (20-73) F 49 (21-76) SAI: M 54 (22-74) F 49 (30-74)	Cross-sectional	Sex- and age-matched controls drawn from the questionnaire-specific reference cohort.	1,2	Patients on current standard replacement suffer from impaired QOL, irrespective of origin of disease.
Gurnell, 2008 (13)	106	44/62	*Mnd (range)* DHEA: 46 (23-65) Placebo: 46 (22-65)	Randomized double-blind placebo controlled	Normative data	1	Subscales on psychological well-being were significantly worse in patients compared to the control population. One subscale of the SF-36 (role emotional) improved significantly after DHEA treatment.
Bleicken[a], 2008 ‡ (10)	210	53/157	*Mnd (range)* PAI: M 41.5 (20-73) F 49 (21-76) SAI: M 54 (22-74) F 49 (30-74)	Cross-sectional	Sex- and age-matched controls drawn from the questionnaire-specific reference cohort.	1,2	SHS seemed equal regarding different glucocorticoid replacement therapies (HC, prednision, cortisone acetate), but was impaired compared to sex- and age-matched controls.

Table 1. Literature overview of studies reporting on psychological functioning, personality, and QoL, in patients with PAI (continued)

Author, year	N	Gender M/F	Age yr	Design	Controls	Domains	Outcomes
Erichsen, 2009 (12)	426	153/273	*Mean (range)* 53 (18-95)	Observational	Normative data	1	QoL is reduced in patients with autoimmune AI, especially in patients with diabetes, whereas thyroid disease did not affect QoL.
Harbeck[a], 2009 (20)	14	3/11	*(range)* (29-70)	Prospective	NA	1,2	Mimicking the physiological rise in cortisol secretion during the night did not affect QoL.
Bleicken[a], 2010a‡ (11)	210	53/157	*Mnd (range)* PAI: M 41.5 (20-73) F 49 (21-76) SAI: M 54 (22-74) F 49 (30-74)	Cross-sectional	Sex- and age-matched controls drawn from the questionnaire-specific reference cohort.	1	QoL was impaired in patients. HC dosages above 30 mg/day were associated with worse SHS. Thrice daily intake of HC was not superior to twice-daily intake.
Bleicken[a], 2010b‡ (53)	216	82/134	*Mean±sd Mnd (range)* PAI: 51±15 48 (20-84) SAI: 57±16 62 (18-81)	Retrospective Cross-sectional	Sex- and age-matched controls drawn from the questionnaire-specific reference cohort.	1,2	Patients showed an impaired SHS compared with controls. Patients who were diagnosed within 3 months showed better SHS.
Warmuz-Stangierska, 2010 (54)	15	2/13	*Mean (range)* 34 (20-49)	Observational	NA	2	Patients demonstrated increased levels of anxiety, fear and over-reaction to stimuli and decreased performance efficacy and need for social contact.
Reisch, 2011 (15)	63	18/45	*Mnd (range)* Men: 43 (25-58) Women: 49 (41-56)	Cross-sectional	Patients with congenital adrenal hyperplasia and sex- and age matched controls from questionnaire specific reference cohorts	1,2	Patients with AD showed more QoL impairments compared to patients with CAH

Table 1. Literature overview of studies reporting on psychological functioning, personality, and QoL, in patients with PAI (continued)

Author, year	N	Gender M/F	Age vr	Design	Controls	Domains	Outcomes
Ekman, 2012 (40)	15	9/6	*Mean (range)* 44.6 (21-74)	Randomized double-blind cross-over	NA	1	QoL did not differ between patients on a four-dose regimen and patients on a two-dose regimen, but patients on a four-dose regimen tended to report better QoL.
Ekman, 2013^ (55)	15	9/6	*Mean±sd* 44.6±15.7	Randomized placebo controlled double-blind cross-over	NA	1	Patients have a dominant Th1 profile that correlates with a reduced QoL.
Langenheim[a], 2013 (56)	14	3/11	*Mean±sd (range)* 63.2±10.0 (47-76)	Cross-over Cross-sectional	Reference data from controls matched by age and sex	1	Compared to the control population, patients reported higher fatigue rates at baseline and at 6 months. Modified-release prednisone showed decreased complaints and fatigue compared to standard prednison treatment.
Meyer, 2013 (44)	200	53/147	*Mnd (range)* 48 (19-90)	Observational	NA	1	QoL was lower in female patients, than in male patients, and it was lower in those with manifestation at older ages and with more autoimmune comorbidities. Latency between first symptoms and diagnosis affected QoL even years after manifestation of disease.
Smans, 2013 (57)	20	8/12	*Mnd (range)* 49.3 (32-66)	Prospective	NA	1	Reducing over replacement in the evening, resulted in a decrease in reported sleep disturbances.
Present study	**54**	**21/33**	*Mean±sd* **49.67±11.8**	**Cross-sectional**	**Healthy controls matched for age, gender and education**	**1,2,3**	**Patients report psychological morbidity and an impaired QoL. Psychological morbidity, impaired QoL, and maladaptive personality traits were associated with higher HC intake.**

*Duplication of cohort which was previously described by Arlt et al., 1999, ‡ Duplication of cohort which was previously by Hahner et al., 2007, ^ Duplication of cohort which was previously by Ekman et al., 2012, † Duplication of cohort which was previously by Heijmans et al., 1998a.

[a] Included both patient with primary adrenal insufficiency and secondary adrenal insufficiency,

AD: Addison's disease; CFS: Chronic Fatigue Syndrome; HC: hydrocortisone; SHS: Subjective Health Status; GHP: General Health Perception; AI: adrenal insufficiency; CAH: congenital adrenal hyperplasia; *Mnd*: Median; *sd*:standard deviation.

Assessed domains: 1 = QoL or QoL related aspects, general well-being, subjective health status; 2 = psychological functioning, psychological morbidity; 3 = personality traits; 4 = personality related aspects (i.e. optimism/pessimism, locus of control); 5 = illness perceptions; 6 = coping strategies.

Considering the limited amount of studies on psychological functioning in patients with PAI and the fact that studies on personality traits are lacking, the aim of the present study was to evaluate psychological functioning and personality traits, as well as QoL in patients with stable treatment for PAI. In accordance to previous studies, we hypothesized that patients with PAI not only would report impaired QoL, but also psychological morbidity, despite long-term stable replacement with hydrocortisone. Furthermore, we hypothesized that patients with PAI demonstrate maladaptive personality traits. The second aim was to explore a potential association between hydrocortisone intake and psychological functioning, personality traits and QoL in patients with PAI.

PATIENTS AND METHODS

Participants

Patients with PAI were recruited via the outpatient clinic of the department Endocrinology of the Leiden University Medical Center (LUMC) and by advertisement via the Dutch Adrenal Patient Society for Addison and Cushing Patients (NVACP; www.nvacp.nl). Thirty-nine patients were derived from the patient network en fifteen patients were derived from the LUMC outpatient clinic. There were no differences regarding gender and age between patients derived from the patient network and patients derived from the outpatient clinic.

Patients with current or previous drug or alcohol abuse or with neurological problems were excluded. A total of 54 participants were included in this study (21 men and 33 women). The mean age of the patients was 50±12 years. Each patient was asked to provide a control person of comparable gender, age (+/- 10 years), and educational level in order to create a control group. The self selection of controls enabled a perfect match for an additional parameter, i.e. social-economic status. Exclusion criteria for controls were present or previous drugs/alcohol abuse or neurological problems.

PAI had been diagnosed based on the classical clinical symptoms and biochemical confirmation of adrenal insufficiency in the presence of increased ACTH concentrations. Adrenal insufficiency was diagnosed when basal cortisol concentrations were below the reference range of normal (<0.12umol/l) or below 500 nmol/l after stimulation with ACTH. Forty-four patients (82%) had been diagnosed with PAI due to autoimmune disease with positive autoantibodies against adrenal cortex, five patients (9%) had been diagnosed with PAI due to non-autoimmune causes (e.g. congenital adrenal aplasia, adrenal calcification), and two patients (4%) were treated with bilateral adrenalectomy for pheochromocytomas. The origin of PAI was unknown for three patients (5%).

The Medical Ethics Committee of the LUMC approved the protocol and written informed consent was obtained from all subjects.

Questionnaires

Both patients and controls were asked to complete the following questionnaires on psychological functioning, personality traits and QoL at home and to return the questionnaires in a prepaid envelope.

The *Apathy Scale* consists of 14 questions on a 4-point scale measuring different features of apathy in the two previous weeks. The score for each item ranges from 0 (no apathy) to 3 (maximum intensity of apathy). The total score ranges from 0-42 points, with higher scores indicating greater apathy. A total score ≥14 points is being used to characterize subjects as apathetic (21,22).

The *Irritability Scale* consists of 14 items measuring different features of irritability in the two previous weeks. The total score ranges from 0-42 points, with higher scores indicating greater irritability. A total score ≥14 points is being used to characterize subjects as irritable (22).

The *Mood and Anxiety Symptoms Questionnaire short-form (MASQ-30)* assesses symptoms that occur in mood and anxiety disorders subdivided into the three subscales negative affect, lack of positive affect and somatic arousal. The scores for each subscale ranges from 10-50, with higher scores indicating more severe negative affect, more positive affect or more somatic arousal. There are no formal cut-off scores (23).

The *Hospital Anxiety and Depression Scale (HADS)* consists of 14 items, and both the anxiety and the depression subscale scores range from 0-21 points. Higher scores indicate more severe anxiety and/or depression. A score >8 points on one of the subscales is being used to characterize subjects as being anxious or depressed, respectively (24,25).

The *Multidimensional Fatigue Inventory (MFI-20)* assesses fatigue. Five different dimensions of fatigue are calculated: 1) General fatigue, 2) Physical fatigue, 3) Reduced activity, 4) Reduced motivation, and 5) Mental fatigue. Scores vary from 0-20; with higher scores indicating greater fatigue (26).

The *Short-Form 36 (SF-36)* assesses functional status and general well-being during the previous month (23;24). The items cover nine health concepts: 1) physical functioning, 2) social functioning, 3) role limitation (physical), 4) role limitation (emotional), 5) mental health, 6) vitality, 7) pain, 8) general health perception, and 9) general perception of change in health. Scores are expressed on a 0–100 scale, and higher scores indicate a better QoL (27,28).

The *EuroQoL-5D (EQ-5D)* assesses current health status reflected in five dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores are expressed on a 1-3 scale per dimension, with higher scores indicating worse QoL. The questionnaire also includes a visual analogue scale (VAS) which comprises a standard vertical 20 cm scale (similar to a thermometer) for recording an individual's rating for their current health-related well-being (29). The VAS score ranges from 0 to 100, with higher scores indicating a better health status.

The *Nottingham Health Profile (NHP)* assesses general well-being and consists of 38 yes/no questions, which are subdivided into six scales assessing impairments, i.e. pain (8 items), energy level (3 items), sleep (5 items), emotional reactions (9 items), social isolation (5 items), and disability/functioning (8 items). Subscale scores are calculated as a weighted mean of the associated items and are expressed as a value between 0-1 (30,31).

The *Physical Symptom Checklist (PSC) assesess* 55 physical symptoms that are mentioned in the DSM-III classification (32). The presence of symptoms is rated on a severity scale from 0 to 3. We excluded the gender specific items (n=4) from the analyses to rule out bias by gender. The total symptom score ranges from 0 to 153. A higher score indicates more (severe) physical symptoms in the preceding week (33).

The *Dimensional Assessment of Personality Pathology short-form (DAPPs)* consists of 136 items to assess personality traits, which are subdivided into 18 subscales: submissiveness, cognitive distortion, identity problems, affective lability, stimulus seeking, compulsivity, restricted expression, callousness, oppositionality, intimacy problems, rejection, anxiousness, conduct problems, suspiciousness, social avoidance, narcissism, insecure attachment, and self-harm. The score for each subscale differs with maxima of 30-40, with higher scores indicating more pronounced maladaptive personality traits (34).

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 20.0.0 (SPSS Inc., Chicago, IL). All data were presented as mean±standard deviations, unless mentioned otherwise. The primary analysis comprised the comparison of scores on the questionnaires between patients with stable treatment for PAI and healthy matched controls. To check the normality of data, the Kolmogorov-Smirnov test was used in addition to histograms and boxplots. Groups were compared using independent samples t-test. A Mann-Whitney U test was used in case of non-parametric data. χ^2 was used in case of categorical data. Because of multiple comparisons, the level of significance for this analysis was set at $P \leq 0.01$. The secondary analysis comprised the relationship between the scores on the various questionnaires and the mean daily dose of hydrocortisone, using a stepwise linear regression model. We included age and gender as additional independent variables. Because of the exploratory nature of this secondary analysis, adjustment of the level of significance for multiple testing was not performed, and the level of significance was set at $P \leq 0.05$.

RESULTS

Sociodemographic and clinical characteristics (Tables 2 and 3)

A total of 54 patients with PAI and 54 healthy controls matched for gender, age, and education, were included. All patients were on stable hydrocortisone and fludrocortisone replace-

ment therapy for a mean duration of 10.1±8.5years (range 2-38 years), as prescribed by their individual physicians (mean daily hydrocortisone intake of 25±7 mg (range 10-50 mg), divided in two to three dosages). Eighty-three percent of the patients also used fludrocortisone in addition to hydrocortisone. Additional medical therapy included DHEA (26% of patients), levothyroxine (46%), anti-hypertensive drugs (13%), and oral contraceptives (9%). Forty-five percent of female patients were postmenopausal.

Table 2. Clinical characteristics

	PAI (n=54)	**Matched controls (n=54)**
Gender (m/f)	21/33	21/33
Age (yrs)	49.67 (11.8)	49.26 (12.5)
Educational level	Low: 10 (19%) Medium: 21 (39%) High: 23 (43%) Unknown: 0	Low: 9 (17%) Medium: 22 (41%) High: 22 (41%) Unknown: 1 (2%)
BMI	26.42 (5.3)	NA
PAI diagnose	Autoimmune: 44 (82%) Non-autoimmune: 5 (9%) Bilateral adrenalectomy: 2 (4%) Unknown: 3 (5%)	NA
Hydrocortisone dose[#]	24.90 (7.2)	NA
Florinef, n (%)	45 (83%)	NA
DHEA, n (%)	14 (26%)	NA
Levothyroxine, n (%)*	25 (46%)	NA
Oral contraceptive, n (%)	2 (11%)	NA
Anti-hypertensives, n (%)	7 (13%)	NA
Menopause, n (%)	15 (45%)	NA

Data are noted in mean (SD) or number and %; PAI, primary adrenal insufficiency, NA, not applicable; #total dose per day; * Hypothyroidism due to M. Hashimoto. Patients with PAI and matched controls did not differ on any characteristic.

Psychological functioning and quality of life (Table 4)

Patients with PAI had a higher total score on the Irritability Scale (P=0.004) compared with matched controls. Patients also showed higher scores on the somatic arousal subscale of the MASQ-30 (P=0.003). Clinically significant apathy and irritability (a score of ≥ 14 on the Apathy Scale and on the Irritability Scale) was present in 35% and 33% of patients, respectively, and significantly more irritability was observed in patients than in controls (P=0.01). On the HADS, 11% of patients had a score of ≥ 8 on the anxiety subscale and 6% on the depression subscale. This is indicative for the presence of clinically relevant anxiety or depression, respectively. There were no significant differences between patients and controls on the depression subscale, anxiety subscale or total HADS score.

Patients scored worse on all subscales of the MFI-20 compared with matched controls, i.e. general fatigue (P<0.001), physical fatigue (P<0.001), reduced activity (P=0.003), reduced motivation (P=0.006), and mental fatigue (P<0.001). Patients with PAI also scored worse on the physical functioning subscale (P<0.001), social functioning subscale (P=0.001), role limitation (physical) subscale (P<0.001), vitality subscale (P=0.009), and general health perception subscale (P<0.001) of the SF-36. On the EQ-5D, patients scored worse than matched controls on activity (P<0.001) and the VAS (P<0.001). Furthermore, patients scored worse on energy (P<0.001) and physical ability (P<0.001) compared with matched controls as measured with the NHP. Lastly, patients reported more general/neurological symptoms (P<0.001), autonomic symptoms (P<0.001), genital symptoms (P=0.002), and feeling hot/cold (P<0.001) on the PSC compared with matched controls.

Personality traits

The scores of the patients on the DAPPs personality traits were not different from those of the matched controls.

The association with daily hydrocortisone intake (Table 5)

Higher hydrocortisone intake was associated with lower psychological well-being, more maladaptive personality traits, and more impaired QoL. More specifically, a higher hydrocortisone dose was associated with more depressive symptoms (HADS Depression subscale, β=0.282, P=0.038), as well as decreased physical functioning (β=-0.365, P=0.008), more

Table 3. Clinical characteristics

	Males with PAI (n=21)	Females with PAI (n=33)
Age (yrs)	48.48 (13.1)	50.52 (11.0)
Educational level	Low: 3 (14%) Medium: 9 (43%) High: 9 (43%)	Low: 7 (21%) Medium: 12 (36%) High: 14 (42%)
BMI	26.12 (3.6)	26.62 (6.3)
PAI diagnose	Autoimmune: 17 (81%) Non-autoimmune: 2 (10%) Bilateral adrenalectomy: 2 (10%) Unknown: 0	Autoimmune: 27 (82%) Non-autoimmune: 3 (9%) Bilateral adrenalectomy: 0 Unknown: 3 (9%)
Hydrocortisone dose#	26.90 (6.8)	23.62 (7.3)
Florinef, n (%)	16 (76%)	29 (88%)
DHEA, n (%)	2 (10%)	12 (36%)
Levothyroxine, n (%)*	6 (29%)	19 (58%)
Oral contraceptive, n (%)	NA	2 (11%)
Anti-hypertensives, n (%)	3 (14%)	4 (12%)
Menopause, n (%)	NA	15 (45%)

Data are noted in mean (SD) or number and %; PAI, primary adrenal insufficiency, NA, not applicable; # total dose per day; * Hypothyroidism due to M. Hashimoto.

Table 4. Psychological functioning, QoL, and personality in patients with PAI

		PAI (n=54)	Matched controls (n=54)	P-value
Irritability scale	Total score	11.32 (7.0)	7.78 (5.3)	0.004
	Score ≥ 14, n (%)	18 (33%)	7 (13%)	0.010
MASQ-30	Somatic arousal	15.49 (7.0)	12.00 (2.6)	0.003
MFI-20	General fatigue	12.15 (5.5)	7.21 (3.5)	<0.001
	Physical fatigue	11.04 (5.1)	6.83 (2.6)	<0.001
	Reduced activity	9.72 (4.1)	7.40 (3.3)	0.003
	Reduced motivation	8.67 (3.5)	6.87 (3.0)	0.006
	Mental fatigue	11.08 (4.4)	7.38 (2.9)	<0.001
SF-36	Physical functioning	80.29 (19.6)	94.15 (7.7)	<0.001
	Social functioning	77.12 (24.5)	91.27 (14.6)	0.001
	Role limitation (physical)	65.28 (43.8)	93.75 (17.8)	<0.001
	Vitality	48.21 (9.8)	52.92 (8.5)	0.009
	General health perception	54.06 (26.1)	77.31 (15.5)	<0.001
EQ-5D	Activity	1.35 (0.5)	1.06 (0.2)	<0.001
	VAS	72.66 (15.9)	84.12 (10.2)	<0.001
NHP	Energy	0.29 (0.4)	0.03 (0.1)	<0.001
	Physical ability	0.09 (0.1)	0.01 (0.0)	<0.001
PSC	General/neurological	0.73 (0.5)	0.35 (0.2)	<0.001
	Autonomic symptoms	0.53 (0.4)	0.16 (0.2)	<0.001
	Genital symptoms	0.29 (0.4)	0.11 (0.2)	0.002
	Feeling hot/cold	0.79 (0.7)	0.27 (0.3)	<0.001

Data are noted in mean (SD), only significant results are listed. Level of significance was set at P≤0.01, adjusting for multiple testing.

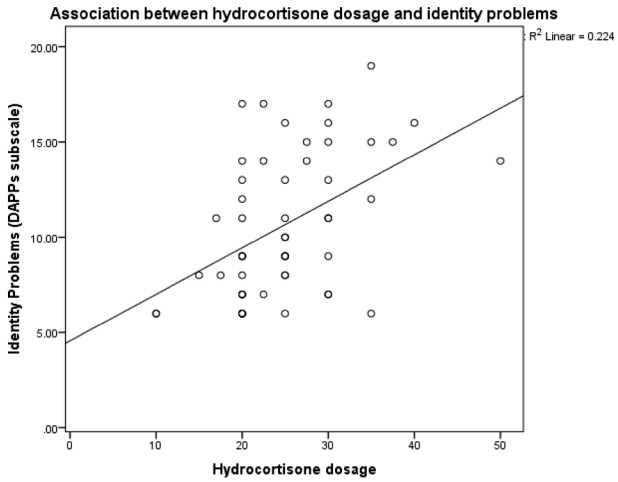

Figure 1. Associations between hydrocortisone dosage and identity problems.

Table 5. Influence of daily hydrocortisone dosage, age, and gender on dimensions in the questionnaires (*P<0.05, **P<0.01)

		Hydrocortisone dosage	Age	Gender
HADS	Depression	β=0.282*		
SF-36	Physical functioning	β=-0.365**		
	Role limitation (physical)	β=-0.329*		
	Vitality			β=-0.284*
	Pain	β=-0.272*		
EQ-5D	Mobility	β=0.345*		
	VAS	β=-0.335*		
DAPP	Cognitive distortion	β=0.288*		
	Identity problems	β=0.474**		
	Compulsivity	β=0.302*		
	Restricted expression	β=0.277*		
	Callousness	β=0.376*		
	Oppositionality	β=0.291*		
	Rejection	β=0.282*		
	Conduct problems			β=-0.358**
	Social avoidance	β=0.316*		
	Narcissism	β=0.273*	β=-0.337*	
	Self-harm		β=0.324*	

Only associations that reached statistical significance (P<0.05) are depicted.
There were no significant associations between daily hydrocortisone dosage, age and gender, and scores on the Apathy scale, Irritability scale, MAQ-30, MVI-20, NHP and PSC.

physical role limitations (β=-0.329, P=0.015) and more pain (β=-0.272, P=0.047) (all SF-36 subscales). Moreover, the SF-36 subscale Vitality was negatively associated with gender (β=-0.284, P=0.039), indicating that females reported less vitality. Furthermore, a higher hydrocortisone intake was associated with worse scores on mobility (β=0.345, P=0.011) and the VAS (β=-0.335, P=0.013) of the EQ-5D. Lastly, a higher hydrocortisone intake was associated with several maladaptive personality traits, including more cognitive distortion (β=0.288, P=0.037), identity problems (β=0.474, P=0.000) (Figure 1), compulsivity (β=0.302, P=0.029), restricted expression (β=0.277, P=0.042), callousness (β=0.376, P=0.005), oppositionality (β=0.291, P=0.035), rejection (β=0.282, P=0.043), social avoidance (β=0.316, P=0.021), and narcissism (β=0.273, P=0.036). Moreover, narcissism was negatively associated with age (β=-0.337, P=0.010) and self-harm was positively associated with age (β=0.324, P=0.017). Female patients reported less conduct problems (β=-0.358, P=0.008).

DISCUSSION

This study demonstrates that patients with stable treatment for PAI suffer from more psychological morbidity with irritability and somatic arousal, in addition to impairments of QoL compared with matched healthy controls. However, personality traits were not different between patients and controls, which indicates that personality traits in patients with PAI, in contrast to psychological functioning, are not sensitive to the effects of a chronic disease, such as PAI and its pharmacological treatment in contrast to psychological morbidity. To our knowledge, this is the first study on personality traits in patients with PAI. Interestingly, there was a strong and consistent association between the mean daily hydrocortisone dose and the prevalence of maladaptive personality traits, like cognitive distortion, identity problems, and compulsivity, and also with restricted expression, callousness, oppositionality, rejection, social avoidance and narcissism. Furthermore, there was a strong positive relation between the mean daily hydrocortisone intake and reported psychological morbidity (i.e. depression) and QoL impairments (i.e. several measures of physical functioning, and pain).

Previous studies by our group have shown similar results with regard to psychological functioning and QoL in patients in long-term remission of Cushing's disease, though patients in remission of Cushing's disease also showed more maladaptive personality traits than their matched controls (3–5,35). These observations suggest that psychological functioning and QoL indeed follow the inverted u-shape dose response curve of cortisol exposure related to MR and GR activation, whereas this is not the case for personality traits and lower cortisol levels. Intriguingly, higher daily hydrocortisone intake seemed to be strongly associated with maladaptive personality traits, indicating that hydrocortisone intake does have a considerable effect on personality traits in patients with adrenal insufficiency.

Our findings regarding QoL are in line with the results of previous studies on decreased QoL in patients with adrenal insufficiency (9,14,36,37) and the self-reported impact of the disease or treatment on subjective health status (38). In addition, several QoL studies demonstrated that inadequate hydrocortisone replacement dosages and, especially, a high hydrocortisone dosages negatively affected QoL (11,37,39,40). Accordingly, we found negative effects of high hydrocortisone intake on QoL in patients with PAI. Intriguingly, we also found a negative effect of high hydrocortisone intake on psychological morbidity and the prevalence of maladaptive personality traits.

In healthy individuals cortisol is secreted in a pulsatile fashion with a superimposed circadian rhythm. It is actually impossible to mimic this normal pattern of hormonal secretion by hydrocortisone replacement. These imperfections in pharmacotherapy are, at least in part, associated with persisted vague complaints and a decreased QoL (9). The importance of mimicking the circadian rhythm of cortisol secretion in patients with adrenal insufficiency, is supported by a study of Johannsson et al., which demonstrated that patients treated with once-daily dual release hydrocortisone tablets, had a more circadian-based cortisol profile, and had more favorable scores on questionnaires assessing psychological well-being and

fatigue, compared to patients treated with conventional hydrocortisone treatment (41). Furthermore, both Lovas et al. (42) and Oksnes et al. (43) reported that continuous hydrocortisone infusion in patients with PAI resulted in cortisol and ACTH levels towards normal circadian levels and positively affected QoL. These two studies suggest that the physiological profile might be related to QoL outcomes.

A previous study by Thomsen et al., (16) reported an increased risk for developing affective disorders (e.g. depression, bipolar disorder) in hospitalized patients with adrenal insufficiency. In our cohort of patients with stable PAI, we did not find differences in depressive symptoms between patients and healthy controls. However, considering the fact that we did find other psychological morbidity (i.e. irritability and somatic arousal), we postulate that even after correction of hypocortisolism, patients with PAI remain vulnerable for developing psychological and, in particular, mood symptoms.

Recently, female gender, manifestation at older age, more autoimmune comorbidities, and latency between first symptoms and diagnosis were found to negatively affect QoL in patients with adrenal insufficiency (44). Our data indicate that the amount of daily hydrocortisone intake should also be included as a potential influencing factor of QoL. Nevertheless, because of the exploratory nature of our study, future research is needed to provide more insight in predictors of reduced QoL in patients with adrenal insufficiency and to further distinguish whether the QoL impairments are caused by the disease itself or its treatment. In addition to the focus on research about somatic predictor variables, researchers should pay attention to potential psychological contributing factors, such as negative illness perceptions and ineffective coping strategies, because recent data have indicated that negative illness perceptions were related to a decreased QoL inpatients in long-term remission of Cushing's diseases (45).

A possible limitation of the present study is the cross-sectional design, which does not preclude that maladaptive personality traits and QoL impairments were already present before onset of the disease. Furthermore, we cannot simply conclude that high hydrocortisone intake causes a decreased QoL, since it might be that high hydrocortisone dosages were prescribed because patients suffered from psychological symptoms or a decreased QoL. Therefore, future studies should use a longitudinal design to enable the evaluation of the course of psychological functioning, QoL, and personality, and of the influence of adaptations in hydrocortisone intake on these three domains over time. A longitudinal design might also elucidate the interesting discrepancy between our finding that personality traits of patients with PAI do not differ from healthy controls, whereas higher daily hydrocortisone intake is significantly associated with maladaptive personality traits in patients with PAI.

In summary, patients with stable treatment for PAI report psychological morbidity and impaired QoL. There is a positive association between the daily hydrocortisone intake and the presence of psychological morbidity, maladaptive personality traits and QoL impairments. These results point toward the possibility to intertwine psychosocial parameters in care for patients with endocrine replacement in general, and for patients with adrenal insufficiency

specifically. This approach would open the area of self-management research in this patient category, which has already been shown to have positive effects on QoL in patients with other chronic somatic diseases (46–48).

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CHAPTER 9

Quality of life (QoL) impairments in patients with a pituitary adenoma: a systematic review of QoL studies

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ABSTRACT

Purpose: Pituitary adenomas give rise to physical and psychological symptoms, which may persist after biochemical cure. Growing attention has been paid to Quality of Life (QoL) in these patients. We aimed to systematically analyze QoL assessment methods and QoL outcome in these patients.

Methods: We conducted a systematic literature search up to January 2014 in PubMed, Web of Knowledge, PsycInfo and EMBASE.

Results: 102 papers assessing QoL in patients with a pituitary adenoma were included. In clinical (original) studies in which QoL was the primary outcome parameter (n=54), 19 studies combined a generic questionnaire with a disease-specific questionnaire. QoL was found to be impaired in patients with active disease relative to controls, and generally improved during biochemical cure. However, no normalization occurred, with patients with remitted Cushing's disease demonstrating the smallest improvement. Somatic factors (e.g. hypopituitarism, sleep characteristics), psychological factors (illness perceptions) and health care environment (rural vs. urban) were identified as influencing factors. Intervention studies (predominantly evaluating medical interventions) have been found to improve QoL.

Conclusions: The growing number of studies assessing QoL generally described the negative impact of pituitary adenomas. QoL research in this patient group could be further elaborated by the development of disease-specific questionnaires for prolactinoma and non-functioning adenoma, consequent use of generic and disease-specific questionnaires and using a long-term (longitudinal) follow-up. Surgical and pharmacological interventions improve but not normalize QoL. We postulate that there might be margin for further improvement of QoL, for instance by using psychosocial interventions, in addition to optimal medical treatment.

INTRODUCTION

Pituitary adenomas can result in classical medical conditions, such as Cushing's disease (CD), acromegaly, non-functioning adenoma (NFA) or prolactinoma. Pituitary adenomas can be treated by transsphenoidal surgery, and some patients undergo additional medical treatment or radiotherapy when needed (1). After successful biochemical treatment many physical, cognitive and psychological symptoms resolve, but may (partly) persist during long-term remission (2).

The research interest for Quality of Life (QoL) in patients with a pituitary adenoma has been emerging in recent years and disease-specific QoL questionnaires have been developed. These disease-specific QoL questionnaires assess QoL aspects relevant to a specific pituitary disease, e.g. ACROQoL for acromegaly (3-5), QoL-AGHDA or the Questions on Life Satisfaction-Hypopituitarism (QLS-H) (6) for growth hormone deficiency (GHD) (7), and the Tuebingen CD-25 and the CushingQoL for CD (8-10). Numerous other QoL questionnaires can assess general QoL domains (generic questionnaires) or a particular domain of QoL, which usually is relevant for more than one illness (e.g. dyspnea, nausea, pain, fatigue) (domain-specific) (11). It is usually recommended that a generic questionnaire is combined with a disease-specific questionnaire, in order to assess both specific characteristics and the general perspective of QoL. This also prevents that unexpected impairments in QoL remain undetected (12). The assessment of QoL is commonly used to evaluate QoL in general or patient populations, to compare treatment in clinical trials, or to support treatment choices in individual patient care (11). The lack of an unambiguous definition of QoL poses major challenge for the evaluation and interpretation of QoL. QoL can be interpreted differently and authors may mean different topics, from different perspectives (13). A commonly used definition is that QoL is "the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient" (13).

Considering the potential short-term, but also long-term negative impact of pituitary adenomas on QoL, the growing attention for QoL in patients with a pituitary adenoma, and the variety of QoL questionnaires available, we aimed to systematically analyze QoL assessment methods and QoL outcome in patients with a pituitary adenoma. Furthermore, we aim to review identified predictors of QoL and potential interventions to improve QoL.

METHODS

Search strategy, eligibility criteria and data extraction

In order to identify papers that examined QoL in patients with pituitary adenomas, we searched Pubmed, Web of Knowledge, PsycInfo and EMBASE up to 16 January 2014. We composed a search strategy focusing on QoL in patients with, or treated for, pituitary adenomas. We used all relevant keyword variations, including free text words. Duplicates were excluded. For the complete search strategy, see Appendix 1. Only original articles were included. Studies were eligible when all of the following criteria were met: 1) addressing patients with pituitary adenomas (CD, prolactinoma, acromegaly, NFA), 2) pituitary disease was not caused by an hereditary component by an hereditary gene mutation (e.g. MEN-I), 3) QoL was assessed and used as a parameter, 4) a clear description of QoL assessment, 5) clear description/presentation of QoL results, 6) groups of pituitary patients > n=10, 7) written in English, and 8) pertaining to adult patients. Reviews, case-reports and letters were excluded. Papers which included patients with pituitary adenomas, but which analyzed data in one group of patients with patients with pituitary adenomas in general (i.e. group consisted of a mixture of patients treated for prolactinoma, craniopharyngioma, non-functioning adenoma, etc.), or combined with patients with other diseases (e.g. other skull based tumors, GHD not related to pituitary adenoma), were not included.

Eligibility and data extraction were assessed by two independent investigators (C.D.A. and A.G.). Inconsistencies were resolved by consensus. The following data were extracted: sample size, gender distribution, disease status (active vs. non-active), design, used QoL scales and outcome.

RESULTS

Identification and selection of literature

The initial search identified 1364 studies, 1237 were excluded based on title and abstract. We retrieved 127 studies for detailed assessment. Twenty-five studies were excluded for the following reasons: no clear description of QoL research (n=6), meeting abstracts (n=5), too small number of included patients (n=8), not original article (n=3), article was not available in English (n=1) or article not available (n=2). Consequently, 102 studies were eligible for inclusion (Figure 1). Based on publication dates of the included articles, it can be seen that over the last decade the number of studies studying QoL assessment in patients with pituitary adenomas has been increasing considerably (Figure 2).

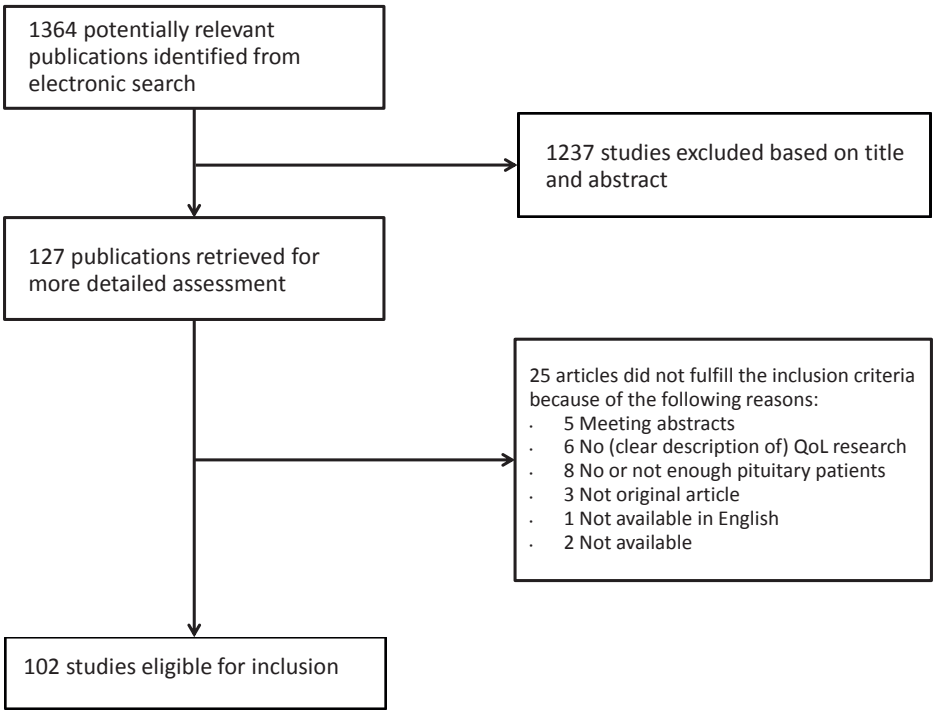

Figure 1. Flow-diagram of article selection.

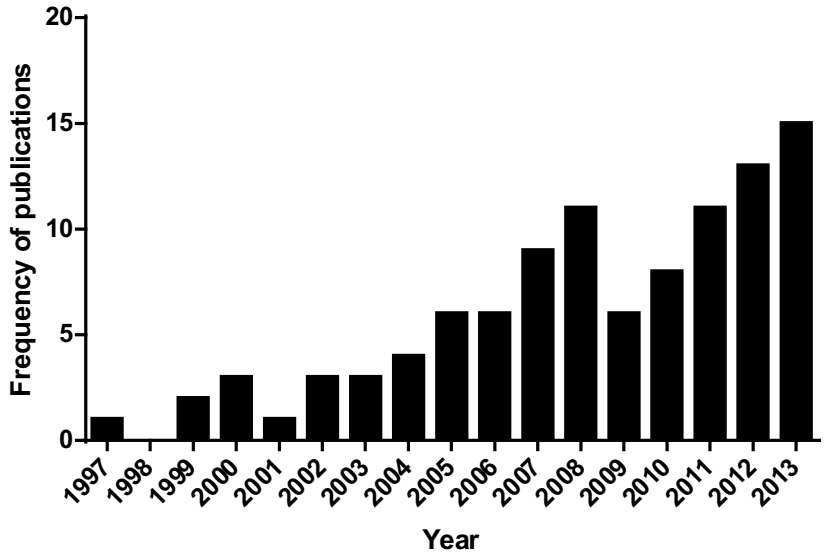

Figure 2. Frequency of QoL studies in patients with pituitary adenomas over the last few decades.

QoL assessment methods

In the 102 studies a total of 49 different questionnaires have been used (10 generic, 9 disease-specific, 30 domain-specific). Sixteen studies assessed QoL with the aim to develop or validate a (disease-specific) questionnaire i.e. the AcroQoL (3-5;14;15), the CushingQoL (8;16-19), the Tuebingen CD-25 (9;10;20) and the QoL-AGHDA (21). Lenderkring et al. developed the Impact on lifestyle Questionnaire and validated it in a group of patients with acromegaly (22). Tiemensma et al. evaluated whether QoL could be assessed with patient's drawing and demonstrated that drawing reflect another dimension (23).

In the other 86 clinical studies, QoL was the primary outcome in 54 studies (63%). Nineteen studies combined a generic with a disease-specific questionnaire. Thirty-four studies (40%) used a domain-specific questionnaire assessing a particular domain, e.g. anxiety and depressive symptoms, pain, fatigue, cognitive failure, sexual function, or social situation. In three studies (5%) QoL was assessed by a simple question or a visual analogue scale (24;25), and in one study the name of the questionnaire was not mentioned (26).

QoL outcome in patients with a pituitary adenoma

Sixty-two studies reported the outcome of QoL in patients with pituitary adenomas i.e. prolactinoma (n=8), NFA (n=16), acromegaly (n=31), and CD (n=24) (Table 1). The majority (n=58, 94%) used a cross-sectional design to compare QoL of patients with pituitary disease to QoL of healthy controls (n=17) reference values (n=13). A minority used patients with other pituitary adenomas (n=6), other patient groups (n=8), or compared patients with the same pituitary disease but with different clinical characters (e.g. male vs. female gender, controlled vs. uncontrolled disease, with or without GHD) (n=16) (findings are described in the next paragraph). Most studies included patients with exclusively controlled disease (n=38, 61%). Eighteen studies (29%) included patients with different diseases stages, i.e. active disease and remission, and five studies (8%) included only patients with active disease. Eight of these studies (13%) were intervention studies which evaluated QoL at baseline.

In eight studies with a total number of 387 patients with prolactinoma, it was demonstrated that patients treated for a prolactinoma reported impairments in QoL, when compared to healthy controls (27-30) and reference values, with most pronounced impairments in mental measures during active disease (31).

Summarizing fourteen studies on 2708 patients with NFA (the number of unique patients might be lower, since two studies reported from the KIMS-database) it can be observed that QoL outcome in patients with NFA demonstrated more diversity. Some studies reported a decreased QoL, relative to healthy controls and reference values (32;33), with most pronounced impairments in physical and mental measures during active disease (31), while others did not find differences in QoL between patients treated for NFA and reference values (30;34;35), or other patient groups (i.e. mastoid surgery vs. NFA surgery, NFA with GHD vs. traumatic brain injury with GHD) (36-38). Compared to patients with GHD due to a craniopharyngioma, male

Table 1. Observational studies in patients with pituitary adenomas

Author, year	N	Gender (M/F)	Disease status	Design	Control group	Scales	Type of Scale	Outcome
Prolactinoma								
Baird et al. (65)*[1]	22	NA	C	C-S	Other pituitary adenomas	SIP List of symptoms and problems specific to patients with pituitary tumors	G, Dis	Patients reported less impairment on each dimension compared to patients with other pituitary adenomas. However, the relative dysfunction was similar for the two groups.
Johnson et al. (31)*	39	15/24	A	C-S	acromegaly/ CD/NFA) Reference values of the normal population	SF-36	G	QoL was decreased, particularly particular mental health.
Heald et al. (63)*	24	13/11	C	C-S	Acromegaly/CD/NFA Normative data	HADS GHQ-28 WHO-QOL-BREF SAS1-2	G, Dos	QoL was similar to patients treated for acromegaly or NFA, and was better compared to patients with CD.
Kars et al. (27)	55	0/55	C	C-S	Age- and gender matched controls	SF-36 NHP MFI-20 HADS	G, Dos	QoL is impaired.
Sonino et al. (29) ^*[1]	52	NA	C	C-S	Controls matched for socio-demographic variables	DSM-IV interview eliciting psychiatric diagnoses DCPR PSI SF-20	G, Dos	Patients reported more stress and psychological distress and less wellbeing (physical functioning, role functioning, social functioning, mental health, health perceptions and pain).
Cesar de Oliveira Natiato et al. (28)	50	0/50	C	C-S	Controls with similar age, SES and geographic distribution	SF-36	G	QoL is impaired in women with prolactinoma treated with dopamine agonists.

Table 1. Observational studies in patients with pituitary adenomas (continued)

Author, year	N	Gender (M/F)	Disease status	Design	Control group	Scales	Type of Scale	Outcome
Van der Klaauw et al. (64)*	128	29/99	C	C-S	Acromegaly/CD/NFA Paragangliomas Controls with similar age and gender distribution	*SF-36* HADS MFI-20 NHP	G, Dos	Patients reported impaired QoL compared to controls, but not compared to patients with paragangliomas. QoL was similar to patients treated for NFA or CD, and better compared to patients with acromegaly.
Raappana et al. (30)*	17	11/6	A/C	C-S	Reference values of the general population	15D	G	Patients reported impairments in QoL
NFA								
Page et al. (36)	48	27/21	C	C-S	Control patients who underwent mastoid surgery Normative data	SF-36 GWBS	G	QoL is impaired.
Johnson et al. (31)*	51	25/26	A	C-S	Acromegaly/CD/ prolactinoma Reference values of the normal population	SF-36	G	Patients reported a decreased QoL, reporting impairment in both physical and mental measures.
Heald et al. (63)*	55	33/22	C	C-S	Acromegaly/CD/ prolactinoma Normative data	HADS GHQ-28 WHO-QOL-BREF SAS1-2 FACT	G, Dos	QoL was similar to QoL of patients treated for acromegaly or prolactinoma, and was better compared to patients with CD
Casanueva et al. (37)Δ	688	438/250	C	C-S	GHD due to TBI	QoL-AGHDA	Dis	QoL of patients with GHD due to NFA were equal to patients with GHD due to TBI or NFA

Table 1. Observational studies in patients with pituitary adenomas (continued)

Author, year	N	Gender (M/F)	Disease status	Design	Control group	Scales	Type of Scale	Outcome
Verhelst et al. (39)	370	185/185	C	C-S	Patients with GHD due to cranio	QoL-AGHDA	Dis	Male patients with GHD due to a cranio reported worse QoL compared to male patients with GHD due to a NFA, whereas female patients with GHD due to a cranio reported a better QoL than female patients with GHD due to an NFA
Dekkers et al. (32)	99	54/45	C	C-S	Controls with similar age and gender distribution	SF-36 HADS MFI-20 NHP	G, Dos	QoL was reduced after successful treatment.
Nielsen et al. (35)	192	116/76	C	O	Age- and sex adjusted normative data.	SF-36 MDI	G, Dos	No differences in QoL. Compared to patients who had undergone transsphenoidal surgery, patients who had undergone craniotomy reported an impaired QoL
Kreitschmann-Andermahr et al. (38)Δ	84	49/35	C	C-S	GHD due to TBI	QoL-AGHDA	Dis	QoL of patients with GHD due to NFA were equal to patients with GHD due to TBI or NFA.
Miller et al. (87)*	48	27/21	C	C-S	Acromegaly Age-adjusted population norms	SF-36	G	QoL was better in patients with NFA compared to patients with acromegaly.
Van der Klaauw et al. (64)*	99	54/45	C	C-S	Acromegaly/CD/prolactinoma Paragangliomas Controls with similar age and gender distribution	*SF-36* HADS MFI-20 NHP	G, Dos	Patients reported impaired QoL compared to controls, but not compared to patients with paragangliomas. QoL was similar to patients treated for prolactinoma or CD, and better compared to patients with acromegaly.
Höybye et al. (60)*Δ	748	456/292	C	C-S	CD matched for age and gender	QoL-AGHDA	Dis	Patients demonstrated a better QoL compared to patients treated for CD
Pereira-Neto et al. (66)*[1]	16	NA	C	C-S	CD (n=5) or acromegaly (n=4)	*SF-36* HIT-6	G, Dos	There were no differences in QoL according to the hormonal profile of the adenoma

Table 1. Observational studies in patients with pituitary adenomas (continued)

Author, year	N	Gender (M/F)	Disease status	Design	Control group	Scales	Type of Scale	Outcome
Biermasz et al. (33)	17	9/8	C	C-S	Controls with similar age, gender and BMI distribution	SF-36 HADS MFI-20 NHP	G, Dos	Patients demonstrated more fatigue and impairments in QoL.
Capatina et al. (34)	193	NA	C	O	Age-related reference values	SF-36 NHP EQ-5D	G	QoL and subjective health was not compromised in patients.
Acromegaly								
Feldt-Rasmussen et al. (46)Δ*	40	14/26	C	C-S	GHD due to several causes	QoL-AGHDA	Dis	Patients with pior acromegaly with current untreated GHD reported worse QoL compared to patients with GHD due to other aetiologies
Johnson et al. (31)*	36	30/6	A	C-S	NFA/CD/ prolactinoma Reference values of the normal population	SF-36	G	Patients reported a decreased QoL, with patients with acromegaly reporting impairment in measures of physical function.
Biermasz et al. (41)	118	61/57	C	C-S	Controls with similar age and gender distribution	SF-36 NHP MFI-20 HADS ACROQoL	G, Dos, Dis	After treatment, patients have a persistently decreased QoL.
Heald et al. (63)*	20	7/13	C	C-S	NFA/prolactinoma/ CD Normative data	HADS GHQ WHO-QOL-BREF SAS1-2	G, Dos	QoL was similar to QoL of patients treated for prolactinoma or NFA, and was better compared to patients with CD.
Kauppinen-Makelin et al. (43)	231	103/128	C	C-S	Sample from the general population with similar age and gender distribution	15-D	G	Patients reported a reduced QoL.

Table 1. Observational studies in patients with pituitary adenomas (continued)

Author, year	N	Gender (M/F)	Disease status	Design	Control group	Scales	Type of Scale	Outcome
Sonino et al. (29)*[1]	10	NA	C	C-S	Controls matched for socio-demographic variables	DSM-IV interview eliciting psychiatric diagnoses DCPR PSI SF-20	G, Dos	Patients reported more stress, psychological stress, abnormal illness behavior and worse QoL (role functioning, social functioning, mental health, health perceptions).
Mattoo et al. (40)	17	11/6	A/C	C-S	Demographically matched controls	PSLES SSQ CSCL DAQ WHO-QoL-BREF GHQ-12 CPRS	G, Dos	Psychiatric morbidity occurs in a significant percentage of patients. Presence of psychiatric morbidity was associated with dysfunction and poorer QoL
Miller et al. (87)*	58	28/30	C	C-S	NFA Age-adjusted population norms	ACROQoL SF-36 AIMS2	G, Dos, Dis	QoL was lower in patients, in comparison with patients treated for NFA. Patients with musculoskeletal pain had more impairment in QoL.
Van der Klaauw et al. (64)*	118	61/57	C	C-S	NFA/CD/ prolactinoma Paragangliomas Controls with similar age and gender distribution	*SF-36* HADS MFI-20 NHP	G, Dos	Patients reported impaired QoL, but not compared to patients with paragangliomas. QoL was worse compared to patients with NFA or prolactinoma.
Leon-Carrion et al. (45)	16	4/12	A		Healthy controls	AcroQoL BDI	Dis, Dos	Compared to healthy controls, acromegalic patients showed higher depression (BDI). ACROQoL scores correlated positively with GH and IGF-I, and negatively with depression measures

Table 1. Observational studies in patients with pituitary adenomas (continued)

Author, year	N	Gender (M/F)	Disease status	Design	Control group	Scales	Type of Scale	Outcome
Psaras et al. (42)*	37	19/18	A/C	C-S	Age-, gender-, and education matched controls	SF-36 SCL-90-R ACROQoL	G, Dis	Patients reported more QoL impairments independent of disease status. Patients without remission reported poorer mental health compared to those with remission.
Raappana et al. (30)	22	12/10	A/C	C-S	Reference values of the general population	15D	G	Patients without suppressive medical treatment had similar QoL compared to the age-standardized general population. Patients needing SA reported QoL impairments.
Valassi et al. (47)*[1]	17	0/17	C	C-S	GHD due to several causes	QoL-AGHDA	Dis	Patients with pior acromegaly with current untreated GHD reported worse QoL compared to patients with GHD due to other aetiologies
Caglar et al. (128)	23	13/10	A	C-S	Gender- and age matched healthy controls	BDI ACROQoL	Dos, Dis	BDI scores did not reveal depression or limited QoL.
Celik et al. (44)	57	0/57	A/C	C-S	Age-, gender and BMI matched healthy controls	ACROQoL BDI FSFI	Dos, Dis	Sexual dysfunction and depression rates were higher in female patients, compared with female healthy controls. There were no differences in QoL between controlled and uncontrolled patients.
Cushing's disease								
Nagesser et al. (26)	44	11/33	C	O	NA	NA	NA	QoL scores were close to optimal, except for mental health and health perception.
Lindholm et al. (58)#	68	NA	C	O	Age and gender adjusted normative data	*SF-36*	G	QoL was impaired, independent of disease control or presence of hypopituitarism.
Hawn et al. (51)#	18	2/16	C	O	Normative data from the general population	SF-36	G	Patients treated with adrenalectomy demonstrated lower QoL.
Feldt-Rasmussen et al. (46)Δ*	135	30/105	C	C-S	GHD due to several causes	QoL-AGHDA	Dis	Patients with CD current untreated GHD reported worse QoL compared to patients with GHD due to other aetiologies

Table 1. Observational studies in patients with pituitary adenomas (continued)

Author, year	N	Gender (M/F)	Disease status	Design	Control group	Scales	Type of Scale	Outcome
Johnson et al. (31)*	42	9/33	A	C-S	Acromegaly/CD/ prolactinoma Reference values of the normal population	SF-36	G	Patients reported a decreased QoL, with patients with patients with patients with CD reporting impairments in all measures.
Heald et al. (63)*	15	5/10	C	C-S	Acromegaly/ prolactinoma/NFA Normative data	HADS GHQ WHO-QOL-BREF SAS1-2	G, Dos	Patients demonstrated impaired psychological well-being and psychosocial functioning compared with patients with other pituitary tumors (acromegaly, NFA, prolactinoma).
Van Aken et al. (54)	58	10/48	C	C-S	Controls with similar age and gender distribution	SF-36 MFI-20 NHP HADS	G, Dos	Patients with long-term remission experience a decreased QoL, with physical and psychosocial impairments, especially in the presence of hypopituitarism.
Lindsay et al. (53)#	23	4/19	A/C	C-S	Age- and gender matched controls from the general population	SF-36	G	Patients demonstrated impaired QoL during active disease, which partly resolves after treatment. However, after long-term follow-up there is still residual impairment.
Sonino et al. (55)#	24	5/19	C	C-S	Controls matched for age, gender, marital status and social class	SRT	G	Patients displayed higher scores in anxiety, depression, psychotic symptoms, with a generalized compromised QoL.
Sonino et al. (29)*[1]	15	NA	C	C-S	Controls matched for socio-demographic variables	DSM-IV interview eliciting psychiatric diagnoses DCPR PSI SF-20	G, Dos	Patients reported more stress, less well-being and worse QoL (physical functioning, role functioning, social functioning, health perceptions).

Table 1. Observational studies in patients with pituitary adenomas (continued)

Author, year	N	Gender (M/F)	Disease status	Design	Control group	Scales	Type of Scale	Outcome
Thompson et al. (61)	39	5/34	C	O	NA	SF-12v2 own Cushing-specific questionnaire	G	The majority of the patients treated with bilateral adrenalectomy fell within the top two thirds of the national average for physical and mental composite score of the SF-12.
Van der Klaauw et al. (64)*	58	10/48	C	C-S	NFA/acromegaly/ prolactinoma Paragangliomas Controls with similar age and gender distribution	*SF-36* HADS MFI-20 NHP	G, Dos	Patients reported impaired QoL compared to controls, but not compared to patients with paragangliomas. QoL was not significantly different from patients with NFA, prolactinoma of acromegaly.
Mattoo et al. (49)	18	4/14	A/C	C-S	Demographically matched controls	PSLES SSQ CSCL DAQ WHO-QoL-BREF GHQ-12 CPRS	G, Dos	Psychological morbidity occurs in a significant percentage of patients. Presence of psychological morbidity is associated with internalizing coping strategies.
Smith et al. (56)	40	6/34	C	O	Population norms	SF-36	G	Patients were below population norms on 7 of 8 subscales of the SF-36. There was no evident difference in QoL between patients treated with laparoscopic or open adrenalectomy.
Ding et al. (50)	43	14/29	A	O	Normative data from the general population	*SF-36*	G	Patients reported that their health status was good to excellent compared with one year before adrenalectomy. However, they showed lower SF-36 scores compared to the general population.
Höybye et al. (60)*Δ	322	84/238	C	C-S	NFA matched for age and gender	QoL-AGHDA	Dis	Patients with CD demonstrated a poorer QoL compared to patients treated for NFA
Psaras et al. (42)*	24	7/17	A/C	C-S	Age-, gender-, and education matched controls	SF-36 SCL-90-R ACROQoL	G, Dis	Patients with and without remission scored poorer on QoL. Patient with remission scored only higher on the subscale emotional role (SF-36) compared to patients without remission.

Table 1. Observational studies in patients with pituitary adenomas (continued)

Author, year	N	Gender (M/F)	Disease status	Design	Control group	Scales	Type of Scale	Outcome
Valassi et al. (96)#	481	91/390	A/C	C-S	Comparison of subgroups of CS due to pituitary, adrenal, ectopic, other cause	CushingQoL EQ-5D	G, Dis	QoL did not differ between subgroups
Alcalar et al. (52)	40	31/9	C	C-S	Demographically matched controls	SF-36	G	QoL and body image were lower in patients. Physical functioning, bodily pain and general health were lower in patients without remission, compared to patients with remission and controls.
Wagenmakers et al. (57)	123	17/106	C	C-S	Controls with similar age and gender	*SF-36* NHP HADS CushingQoL	G, Dos, Dis	Patients reported a worse QoL.
Abraham et al. (59)#	66	14/52	A	C-S	Obese subjects	*SF-36* Locally developed CS symptom questionnaire	G, Dis	QoL was lower in patients, than in obese individuals. After adjusting for symptom count, obese individuals showed worse on mental health scores then the CS population.
Van der Pas et al. (48)	17	4/13	A	C-S	Age-adjusted literature derived reference values	SF-36 NHP HADS MFI-20 CushingQoL	G, Dos, Dis	Patients demonstrated impaired QoL.

* Also included groups of patients with other pituitary diseases
*[1] Also included groups of patients with other pituitary diseases, but other groups were <10 or mixed with other diseases, therefore not mentioned in other tables
Also patients with adrenal Cushing's syndrome included
^ Also patients with idiopathic hyperprolactinaemia included
ΔKIMS-database
Disease status: A=active disease, C=controlled disease
NA=not applicable
Types of scales: G=Generic, Dis=Disease specific, Dos=Domain specific
SF-36: included in spider-plots, *SF-36:* not included in spider plots, because mean scores on a 0-100 scale were not presented.
GHD: growth hormone deficiency; GH: growth hormone; RT: radiotherapy; CD: Cushing's disease; Cranio: craniopharyngioma
Design: C-S: cross-sectional; O: Observational
For a list of abbreviated questionnaire names, see table 3.

patients with GHD due to a NFA reported a better QoL, whereas female patients with GHD due to a NFA reported worse QoL (39).

Evaluating fifteen studies on acromegaly with a total number of 820 patients, it was demonstrated that patients with active, as well as controlled acromegaly reported more impairments in QoL, relative to healthy controls and reference values (29-31;40-43) which encompassed depressive symptoms and sexual dysfunction (44;45). Furthermore, patients with prior acromegaly with current untreated GHD reported worse QoL compared to patients with GHD due to other aetiologies (46;47).

Summarizing twenty-two studies on CD with a total number of 1713 patients, it can be observed that in patients with active, as well as controlled disease, QoL was impaired compared with healthy controls and reference values (29;31;42;48-58). Abraham et al. compared QoL of patients with active CD, with that of obese individuals, and demonstrated a reduced QoL in CD (59). Furthermore, patients with CD with current untreated GHD reported worse QoL than counterparts with GHD due to other aetiologies (46;60). Other studies reported a less negative effect on QoL, among which the study of Negasser et al. reporting that after treatment of CD, QoL scores were close to optimal, except for mental health and health perception (26). Furthermore, Thompson et al. reported that the majority of the patients treated with bilateral adrenalectomy fell within the top two thirds of the national average for physical and mental composite domains (SF-12) (61).

Studies comparing groups of patients with different pituitary adenomas demonstrated that either patients with CD (31;60;62;63) or patients with acromegaly have worse QoL relative to NFA and prolactinoma patients (64;65). A single study did not find differences between patients treated for NFA (n=16) and small groups of patients treated for CD (n=5) or acromegaly (n=4) (66).

Spider plots of studies reporting results of the Short-Form 36 health survey (SF-36)

The SF-36 was the most frequently used generic questionnaire (n=44, 43%), and therefore, we created spider plots to represent the average QoL outcome as assessed with the SF-36 (Figure 3a-d). Twenty-eight studies (28%) reported the mean and standard deviation of the SF-36 subscales and we calculated the average score on each subscale, categorized per disease (acromegaly, CD, NFA, prolactinoma) and disease status (non-treated/treated) (Appendix 1). Scores of a Dutch sample of healthy controls (67) were also represented in the spider-plots (Dutch data were comparable to normative data of other countries (68-72)).

Examining the four spider plots it can be observed that during active disease patients with CD report most impaired QoL. During remission, patients with CD still report the worst QoL when compared to the other three groups, followed by patients with acromegaly. When comparing QoL in groups of active/non-treated patients, with QoL in groups of controlled/treated patients, it can be seen that QoL generally improves after treatment in patients with a pituitary adenoma. Apparently, the smallest improvement can be seen in patients with CD.

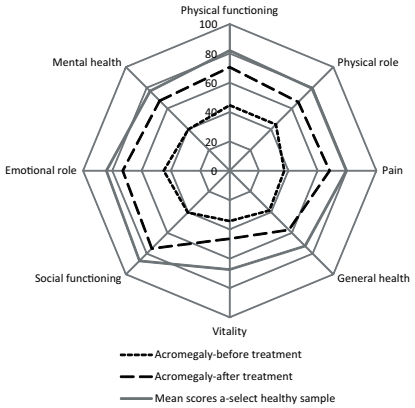

Figure 3a. SF-36 scores in patients with acromegaly

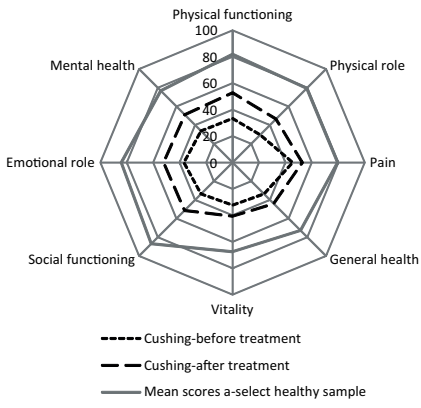

Figure 3b. SF-36 scores in patients with Cushing's disease

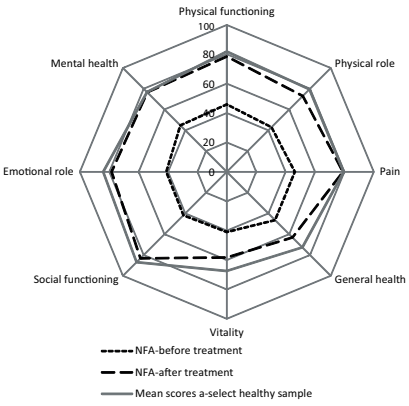

Figure 3c. SF-36 scores in patients with NFA

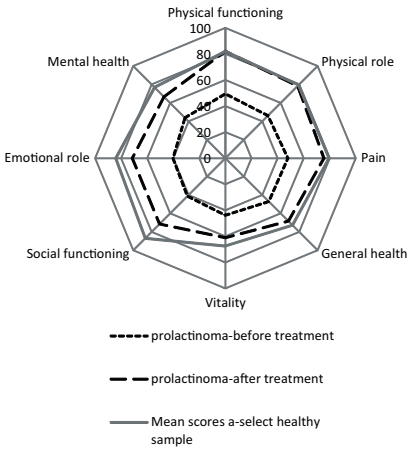

Figure 3d. SF-36-scores in patients with Prolactinoma

Acromegaly-before treatment: Johnson et al. (31), Psaras et al. (42), Milian et al. (62); *Acromegaly-after treatment:* Biermasz et al. (41), Biermasz et al. (86), Miller et al. (113), Van der der Klaauw et al. (91), Wexler et al. (79), Wassenaar et al. (85), Psaras et al. (42), Valassi et al. (47), Postma et al. (92), Milian et al. (62), Miller et al. (87); *Cushing's disease-before treatment:* Johnson et al. (31), Lindsay et al. (53), Psaras et al. (42), Van der Pas et al. (48), Milian et al. (62); *Cushing's disease-after treatment**: Van Aken et al. (54), Lindsay et al. (53), Smith et al. (56), Psaras et al. (42), Hawn et al. (51), Tiemensma et al. (23); *NFA-before treatment:* Johnson et al. (31); *NFA-after treatment:* Page et al. (36), Dekkers et al. (32), Van Beek et al. (75), Nielsen et al. (35), Miller et al. (87), Biermasz et al. (33), Capatina et al. (34); *Prolactinoma-before treatment:* Johnson et al. (31); *Prolactinoma-after treatment:* Kars et al. (27), Cesar de Oliveira Natiato et al. (28); mean scores a-select sample: mean scores of an a-select group of individuals in The Netherlands. *The study of Alcalar et al. (52) was not included for the spider plots, because SF-36 scores were that low (range), that it can be questioned whether SF-36 was scored adequately.

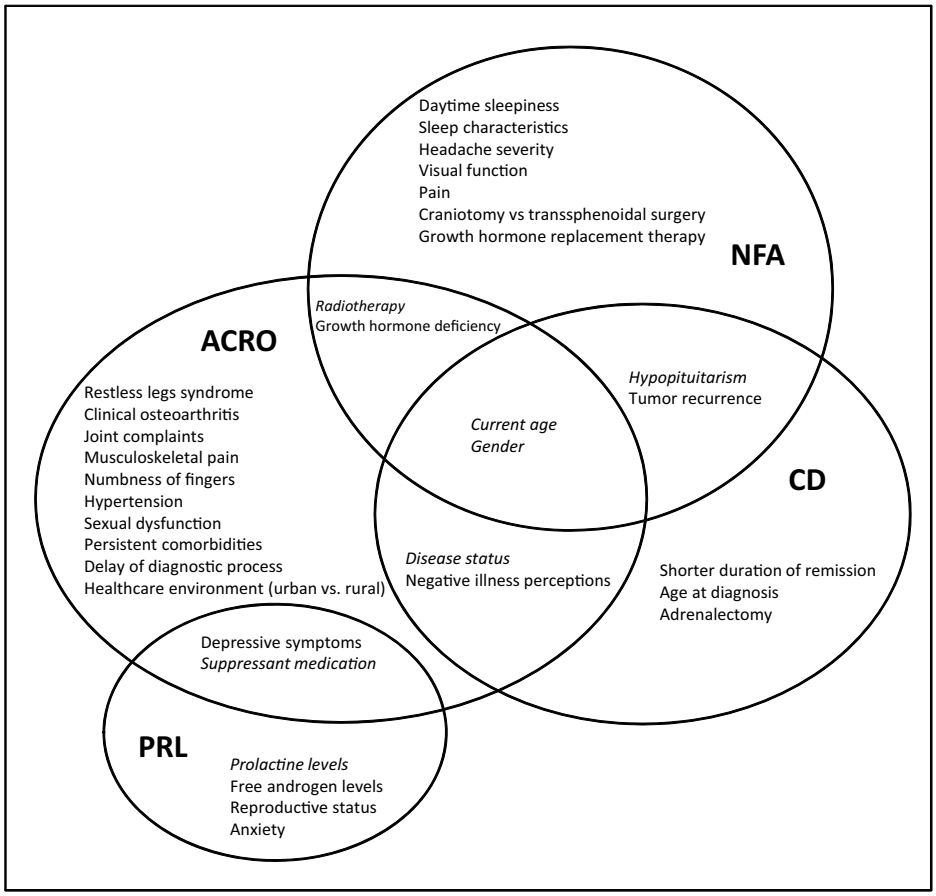

Figure 4. Influencing factors.
Factors which have been found to significantly influence QoL. Normal: consistent between studies. *Italian:* inconsistent between studies. ACRO: acromegaly, NFA: non-functioning pituitary adenoma, CD: Cushing's disease; PRL: prolactinoma.

When comparing the average QoL of patients after treatment, with QoL of an a-select healthy Dutch sample, it can be seen that QoL does not normalize after treatment. Nevertheless, in patients after treatment for NFA or prolactinoma some subscales were equal to the mean scores of this a-select sample (i.e. NFA: Mental health, Pain; prolactinoma: Physical functioning, Physical role).

Influencing factors

Fifty-six studies (55%) described influencing factors on QoL in patients with a pituitary adenoma. A great variety of influencing factors has been reported, with same factors being relevant for two or more types of pituitary adenomas, such as current age and gender, while others were only relevant for one specific pituitary adenoma (Figure 4).

In patients treated for prolactinoma, prolactin levels and free androgen levels were negatively associated with reported QoL (28), whereas others found no correlation with hyperprolactemia (27;30). Furthermore, a negative influence was found for problems in reproductive status and higher anxiety and depression levels (27), and present use of dopamine agonists (DA) (30), whereas others found no significant effect of DA use (27;64), nor a significant effect of tumor size (micro/macro) (64).

Factors that negatively influenced QoL in patients with NFA were impairments in visual function, pain (34;73), sleep disturbances (33), daytime sleepiness (74), older age, female sex, tumor recurrence, hypopituitarism (32;34;36;73;75), and radiotherapy therapy (36;73), whereas in other studies no significant influence of pituitary deficiency (30;36) or radiotherapy was observed (30;32;75). Interestingly, Capatina et al. reported a positive effect of non-replaced GHD on QoL (34). Patients treated with craniotomy reported more QoL impairments relative to patients who had undergone transsphenoidal surgery (35).

In patients with acromegaly, an uncontrolled disease status or biochemical activity (e.g. high IGF-I levels) were found to negatively influence QoL (43;45;76-79), whereas other studies did not find this association (30;42;44;78;80-83). Other negatively influencing factors were radiotherapy (30;42;44;78;80-83), restless leg syndrome (84), clinical osteoarthritis (85), joint complaints (86) musculoskeletal pain (42;86;87), numbness of fingers, hypertension (88), sexual dysfunction (44), depressive symptoms (45;47;81), GHD (79;89;90), and persistent comorbidities (42). Most studies reported the negative effect of female gender (62;64;83;91;92), whereas one study reported the negative effect of male gender (30). As expected, current older age was found to negatively influence QoL (41;43;47;62;64;85;86;91). Medical treatment for acromegaly was negatively associated with QoL (30;78;82;92). Patients only treated with surgery reported a better QoL relative to patients treated with surgery and medical treatment (93), whereas others found no effect of medical treatment versus treatment with surgery and/or radiotherapy (64). In addition, delay of the diagnostic process (>1 year) and living in an urban health care environment (instead of rural health care environment) were also found to be disadvantageous (94). In 2011, researchers of our group demonstrated that in patients with long-term remission of acromegaly also psychological factors (i.e. negative illness perceptions) negatively influenced QoL (95).

In patients with remission of CD, shorter duration of remission (53;57), female gender (54;54;57) older age and older age at diagnosis, and hypopituitarism (54) were found to negatively influence QoL, while Psaras et al. found that younger age and not undergoing reoperation were found to be negatively associated with QoL (42). Others reported no association with hormonal deficiencies, etiology of CS (pituitary- or adrenal-dependent), treatment strategies (53;57;96), and current disease status (42). On the other hand, Alcalar et al. did demonstrate that the scores for physical functioning, bodily pain, and general health were all lower in patients without remission, when compared to those in remission (52). The positive influence of treatment with adrenalectomy was reported (24;26;51;56;61) without

Table 2. Intervention studies aiming to improve QoL

Author, year	N	Disease	Disease status	Design	Intervention	Scales	Type of Scales	Positive effect on QoL?
Surgery								
Pikkarainen et al. (25)#	74	CD/CS	C	Ret	Treatment of CS in general	VAS questionnaire dealing with symptoms	Dos	Yes
Lindsay et al. (53)	23	CD	A/C	P	TSS	SF-36	G	Yes
Tanemura et al. (73)	30	NFA	A/C	P	TSS	*SF-36* GHQ-30 NRS-pain	G, Dos	Yes
Milian et al. (62)	94	ACRO/ CD/ PRL/NFA	A/C	C-S F-U	Surgical treatment.	SF-36 SCL-90-R QLS-H ACROQoL	G, Dis	Yes
Pharmaceutical interventions								
Biermasz et al. (107)	14	ACRO	C	P	Increasing dose interval from 4 to 6 weeks within sandostatin LAR treatment	NHP	G	No
Neggers et al. (104)	20	ACRO	C	D-B P-C C-O	Additional weekly Pegvisomant next monthly SSA therapy vs. placebo	ACROQoL PASQ	Dis	Yes
Madsen et al. (105)	18	ACRO	C	R C-O	Co-treatment with Pegvisomant vs. unchanged SA monotherapy	EQ-5D PASQ	G, Dis	No
Lombardi et al. (99)	51	ACRO	A	F-U	long-acting Lanreotide Autogel	NHP	G	Yes
Schopohl et al. (106)	37	ACRO	C	P	Lanreotide Autogel	ACROQoL	Dis	No
Mangupli et al. (100)	28	ACRO	C	F-U	Octreotide-LAR therapy	ACROQoL	Dis	Yes
Karaca et al. (101)	22	ACRO	A	R	Octreotide LAR vs. surgery	ACROQoL	Dis	Yes (both groups)

Table 2. Intervention studies aiming to improve QoL (continued)

Author, year	N	Disease	Disease status	Design	Intervention	Scales	Type of Scales	Positive effect on QoL?
Trainer et al. (103)	84	ACRO	C	O-L R C	Pegvisomant vs. Pegvisomnt+LAR	ACROQoL EQ-5D	G, Dis	Yes
Ghigo et al. (102)	113	ACRO	A	R O-L	Pegvisomant vs. octreotide LAR	ACROQoL SSS	Dis	Yes (both groups)
Sonino et al. (98)	10	ACRO	A	P	slow-release lanreotide	KSQ CSKSLPP MSSQ	Dos	Yes
Fleseriu et al. (108)#	50	CD/CS	C	O-L F-U	Mifepristone	*SF-36* BDI	G, Dos	Yes
Katznelson et al. (109)#	46	CD/CS	A	O-L F-U	Mifepristone	*SF-36*	G	Yes
Van der Pas et al. (48)	17	CD	A	P	Stepwise medical therapy	SF-36 NHP HADS MFI-20 CushingQoL	G, Dos, Dis	No
Growth hormone replacement therapy								
Casanueva et al. (37)Δ	688	NFA	C	P C-S	GHRT	QoL-AGHDA	Dis	Yes
Verhelst et al. (39)	370	NFA	C	P C-S	GHRT	QoL-AGHDA	Dis	Yes
Svensson et al. (111)Δ	380	NFA	C	P C-S	GHRT	QoL-AGHDA	Dis	Yes
Kreitschmann-Andermahr et al. (38)Δ	84	NFA	C	P C-S	GHRT	QoL-AGHDA	Dis	Yes

Table 2. Intervention studies aiming to improve QoL (continued)

Author, year	N	Disease	Disease status	Design	Intervention	Scales	Type of Scales	Positive effect on QoL?
Van der Klaauw et al. (112)	16	ACRO	C	P	GHRT	HADS MFI-20 NHP QoLAGDHA	G, Dos, Dis	No
Miller et al. (113)	30	ACRO	C	R P-C	GHRT	SF-36 QoL-AGHDA SQ	G, Dos, Dis	Yes
Valassi et al. (47)*[1]	17	ACRO	C	R P-C C-S	GHRT	SF-36 QoL-AGHDA SQ	G, Dos, Dis	Yes
Giavoli et al. (110)*	22	ACRO/ NFA	C	C-S F-U	GHRT	QLS-H	Dis	Yes
Feldt-Rasmussen et al. (46)Δ*	175	ACRO/ CD	C	C-S P	GHRT	QoL-AGHDA	Dis	No
Höybye et al. (60)*Δ	1070	CD/NFA	C	C-S P	GHRT	QoL-AGHDA	Dis	Yes
Other interventions								
Hatipoglu et al. (114)	20	ACRO	C	P C	Exercise program	ACROQoL BDI MBSRQ	Dos, Dis	Yes

* Also included groups of patients with other pituitary diseases

*[1] Also included groups of patients with other pituitary diseases, but other groups were <10 or mixed with other diseases, therefore not mentioned in other tables

Also adrenal Cushing included

ΔKIMS-database

Disease status: A=active disease, NA=non-active disease

SF-36: included in spider-plots, *SF-36:* not included in spider plots, because mean scores on a 0-100 scale were not presented.

GHD: growth hormone deficiency; GH: growth hormone; GHRT: growth hormone replacement therapy; RT: radiotherapy; CD: Cushing's disease

Design: Design: C-S: cross-sectional; P: Prospective; F-U: Follow-Up; R: randomized; C: controlled; P-C; placebo-controlled; O-L; open-label; D-B; double-blind; N-C: non-comparative; Ret: retrospective; C-O: cross-over

For a list of abbreviated questionnaire names, see table 3.

differences in laparoscopic adrenalectomy versus open adrenalectomy (50). In addition, psychological factors (i.e. negative illness perceptions) were also reported to be negatively related to QoL in patients in remission of CD (97).

Interventions (Table 2)

Twenty-eight intervention studies used QoL as an outcome parameter, including six randomized studies, three placebo controlled studies, and six follow-up studies using more than two measurement time points. In 11 studies QoL was the primary outcome parameter. Apparently, there were no intervention studies in patients with prolactinoma using QoL as an outcome parameter.

Surgery (n=4)

Four studies including 221 patients evaluated the effect of surgery. In patients with NFA, QoL increased after surgery (6 months) (73). Milian et al. reported that QoL improved within 3 months after surgery in patients with a pituitary adenoma and a trend was found for further amelioration at 12 months after surgery (62). In patients with CD, surgical treatment (transsphenoidal, as well as adrenalectomy) was found to improve QoL (25;53).

Pharmaceutical interventions (n=23)

Twenty-three studies evaluated the effect of pharmaceutical interventions (other than growth hormone replacement therapy), including a total of 464 patients. The majority of the intervention studies evaluated the effect of medical treatment in patients with acromegaly. Treatment with long-acting Lanreotide improved QoL in patients with active acromegaly (98-100). However, Karaca et al. did not find differences in improvements in QoL after treatment with Octreotide LAR compared to surgery (101). Furthermore, no differences were found between naïve patients treated with octreotide LAR and naïve patients treated with Pegvisomant (102). In addition, QoL improvements have been reported after treatment with Pegvisomant, or combination therapy (Pegvisomant/LAR) in patients with controlled acromegaly (103). Moreover, a placebo controlled study demonstrated the positive effect of combination therapy (somatostatine analog+Pegvismant) vs. monotherapy (somatostatine analog+placebo) (104), whereas others did not find significant improvement of QoL after cotreatment with Pegvisomant in addition to the usual treatment with somatostatine analog (105). There were no differences found in QoL in patients who previously used Octreotide LAR, who switched to Lanreotide autogel (106). Biermasz et al. examined whether the interval between sandostatin LAR injections could be increased and demonstrated that there were no differences in QoL during withdrawal after an injection up to 8 weeks (107).

In patients with CD the relatively new treatment with glucocorticoid receptor antagonist (Mifepristone) was found to positively affect QoL (108;109). Recently, Van der Pas et al. evaluated the effect of a stepwise medical treatment (i.e. pasireotide, cabergoline, ketoconazole)

on QoL in patients with de novo, residual or recurrent CD and reported no improvement in QoL (except for emotional reaction) (48).

Ten studies investigated the effect of GH replacement therapy, covering a total sample size of 2852 patients. The number of unique patients might be lower, since two studies reported from the KIMS-database. It was reported that GH replacement therapy positively affects QoL

Table 3. List of abbreviated questionnaire names

Type of scale	Name
Generic	**SF-20/36/SF-6D:** Short-Form health survey **(P)GWBS:** (Psychological) General Well-Being Schedule **NHP:** Nottingham Health Profile **EQ-5D:** European Quality of Life Scale **GHQ-12/28/30:** General Health Questionnaire-28/30 **WHO-QOL-BREF:** World Health Organization Quality of Life Scale-abbreviated version **SIP:** Sickness Impact Profile **15D:** producing a 15-dimensional profile and a single index score **SCL-90 (-R):** Symptom Checklist 90 (revised) **SRT:** symptom rating test
Disease-specific	**ACROQoL:** Acromegaly Quality of Life Questionnaire **SSS:** Signs and Symptoms Scale-acromegaly **PASQ:** Patient-assessed-Acromegaly Symptom Questionnaire **QLS-H:** Questionnaire of Life Satisfaction-Hypopituitarism **CushingQOL:** Cushing Quality of Life questionnaire **Tuebingen CD-25:** Tuebingen Cushing's disease quality of life inventory **QoL-AGHDA:** Quality of Life Assessment of Growth Hormone Deficiency in Adults
Domain-specific	**HADS:** Hospital Anxiety Depression Scale **MFI-20:** Multidimensional Fatigue Inventory **MDI:** Major Depression Inventory **NRS-pain:** Numerical Rating Scale-pain **CFQ:** Cognitive Failure Questionnaire **FACT:** Functional Assessment of Cancer Therapy **SAS 1-2:** Social Adjustment Scale-modified **FSFI:** Female Sexual Function Index **SSQ:** Social Support Questionnaire **SQ:** Symptom Questionnaire (anxiety, depression, somatic symptoms, anger/hostility) **BDI:** Beck Depression Inventory **MBSRQ:** Multidimensional Body-Self Relations Questionnaire **PSLES:** Presumptive Stressful Life Events Scale **HIT-6:** Headache Impact Test scale **CSCL:** Coping Strategies Check List **AIMS2:** Arthritis Impact Measurement Scale 2 **CSKSLPP:** Cognitive Scale of Kellner's Screening List for Psychosocial Problems **CPRS:** Comprehensive Psychopathological Rating Scale **MSSQ:** Marks' Social Situation Questionnaire **KSQ:** Kellner's Symptom Questionnaire (psychological distress, well-being) **DCPR:** Diagnostic Criteria for Psychosomatic Research (irritable mood, demoralization, persistent somatization) **PSI:** Psychosocial Index (chronic stress, psychological distress, abnormal illness behavior, psychological well-being) **DAQ:** Dysfunction Analysis Questionnaire (social, vocational, personal, family, cognitive)

in patients with GHD due to a prior NFA (37-39;60;110;111). In patients with GHD due to prior acromegaly, some studies reported no effect of GH replacement therapy (46;112), whereas others did find a positive effect of GH replacement therapy in these patients (47;110;113). Some studies reported that QoL improves after GH replacement therapy in patients with GHD due to prior CD (60), whereas other studies did not report this improvement (46).

Other interventions (n=1)

Interestingly, a recent study of Hatipoglu et al. evaluated the potential beneficial effects of physical exercise on perceived body-image and QoL in acromegalic patients (n=20). They demonstrated that an exercise program positively affected self-assessed body-image, but that it did not affect QoL or depressive symptoms (114).

DISCUSSION

This first systemic review on QoL research in patients with a pituitary adenoma showed that there is considerable variation in used questionnaires and combinations of questionnaires. It demonstrated the negative impact of pituitary adenomas on QoL, with patients with acromegaly or Cushing's disease generally demonstrating the most impaired QoL. The cause of this (persistent) impairment in QoL seems to be multi-factorial, since a variety of somatic, psychological and environmental factors are found to influence QoL. A relatively small number of studies evaluated interventions aiming to improve QoL. Intervention studies, predominantly evaluating medical interventions, have been demonstrated to improve QoL, but no normalization occurs, with patients biochemically cured for CD demonstrating the smallest improvement in QoL relative to patients with active disease.

Patients with acromegaly or Cushing's disease generally reported the most impairment in QoL relative to patients with prolactinoma or NFA. This observation is in accordance with the findings of Van der Klaauw et al. which demonstrated that patients in remission of acromegaly had the most impaired overall QoL, followed by Cushing's disease, prolactinoma and NFA (64). We speculate that these differences could be explained by the fact that these patients have not been exposed to elevated hormone secretion and therefore, probably experience less severe consequences. Nevertheless, a disease-specific QoL questionnaire for NFA is lacking, which for instance should assess visual dysfunction, a common symptom which has been found to contribute to QoL in patients with NFA (73). Therefore, it could be that the impact of NFA is underestimated by the currently available QoL studies. Until a disease-specific questionnaire is available, QoL studies in patients with NFA should take into consideration the assessment of domain-specific questionnaires, such as the National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) (115;116).

The majority of the predictors identified in the available literature consist of somatic factors, and surgical and pharmacological interventions targeting these somatic factors have

been found to improve QoL. However, the effects of some medical interventions for pituitary disease, such as replacement therapy for hypopituitarism, have not yet been evaluated. As illustrated by the spider-plots (figure 3a-d), there might be room for further improvement in QoL for patients with pituitary diseases. Tiemensma et al. demonstrated negative illness perceptions and ineffective coping strategies in patients with pituitary disease (95;97). They postulated that these psychological aspects could be a potential target for improving QoL and the authors point toward the potential beneficial effect of psychosocial interventions, adapting illness perceptions and coping strategies, next to medical treatment. Until now, there is only one pilot-study which described the efficacy of a 26-week patient education intervention for patients with neuroendocrine tumors. This program mainly focused on enhancing self-efficacy (117). The results of this study demonstrated that perceived stress decreased and self-efficacy and physical functioning (SF-36) improved after the intervention (118). Although the efficacy of psychosocial interventions should be further investigated in a randomized controlled trial in a homogenous group of patients with a pituitary adenoma, this study provided promising data for the efficacy of psychosocial interventions for the improvement of QoL in patients treated for pituitary adenomas.

When examining the selected QoL studies, some interesting facts can be observed. For instance, the number of studies assessing QoL differs considerably between the four patient populations, with the largest number of studies in patients with acromegaly, followed by Cushing's disease and NFA, and the smallest number in patients with prolactinoma. This is in particular interesting, considering the fact, that prolactine hypersecretion is most common in pituitary adenomas (119). Future research should focus on QoL in this under-evaluated group. It should be noted that some papers were not selected for the present review, because they did not met inclusion criteria for this review, although they did measure QoL related aspects (e.g. general well-being (120), psychological symptoms (121)). Furthermore, studies with patients with other pituitary tumors were also not selected for the present review, although they did measure important QoL-related factors, such as personality traits, psychopathology (122-125) and perceived health (126). A relatively small number of studies evaluated interventions aiming to improve QoL in patients with pituitary disease, in contrast to the large number of observational studies reporting the impairments in QoL. Furthermore, the number of studies examining QoL in naïve patients is quite small. In addition, only a few studies evaluated QoL in patients during long-term follow-up. More longitudinal studies including naïve patients are needed to provide more information about the time course of QoL in patients with pituitary diseases.

The definition of QoL in the book of Spilker stresses the importance of the patient perspective of QoL (13). During a recent focus group study of our research group we elucidated the patient perspective of QoL. This study identified QoL aspects which are not (yet) covered by available disease-specific QoL questionnaires (127), such as visual problems, issues with a changed personality, feelings of frustration, and a reduced social network. Therefore, it might

be suggested that the available QoL questionnaires can be further elaborated by including the patient perspective. Furthermore, disease-specific QoL questionnaires for NFA, prolactinoma or pituitary diseases in general should be developed, in order to further improve the quality of QoL research is patients with a pituitary adenoma.

In conclusion, the growing number of studies using QoL assessment in patients with a pituitary adenoma generally described the negative impact of these medical conditions on QoL of the patients afflicted. QoL research in this patient group could be further elaborated by the development of disease-specific questionnaires, consistent use of generic, as well as disease-specific questionnaires, evaluating naïve patients and using a long-term follow-up. Surgical and pharmacological interventions have been demonstrated to improve QoL. Nevertheless, considering the multi-factorial determination of QoL, we postulate that there is substantial room for further improvement of QoL, by for instance using psychosocial interventions, besides optimal medical treatment.

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APPENDIX 1. SEARCH STRATEGY

PubMed:

("Pituitary Neoplasms"[mesh] OR "Pituitary Neoplasms"[all fields] OR "Pituitary Neoplasm"[all fields] OR "Pituitary Tumors"[all fields] OR "Pituitary Tumor"[all fields] OR "Pituitary Adenomas"[all fields] OR "Pituitary Adenomas"[all fields] OR "ACTH-Secreting Pituitary Adenoma"[all fields] OR "ACTH-Secreting Pituitary Adenomas"[all fields] OR "Corticotroph Adenoma"[all fields] OR "Corticotroph Adenomas"[all fields] OR "Cushing syndrome"[mesh] OR "Cushing syndrome"[all fields] OR "Cushing's Syndrome"[all fields] OR "Hypercortisolism"[all fields] OR "Cushing disease"[all fields] OR "Cushing's disease"[all fields] OR "Growth Hormone-Secreting Pituitary Adenoma"[all fields] OR "Growth Hormone-Secreting Pituitary Adenomas"[all fields] OR "Acromegaly"[all fields] OR "Prolactinoma"[all fields] OR "Prolactinomas"[all fields] OR "Microprolactinoma"[all fields] OR "Microprolactinomas"[all fields] OR "Macroprolactinoma"[all fields] OR "Macroprolactinomas"[all fields] OR "non-functioning adenoma"[all fields] OR "non-functioning adenomas"[all fields] OR "non-functioning pituitary adenoma"[all fields] OR "non-functioning pituitary adenomas"[all fields] OR "non-functioning macroadenoma"[all fields] OR "non-functioning macroadenomas"[all fields] OR "nonfunctioning adenoma"[all fields] OR "nonfunctioning adenomas"[all fields] OR "nonfunctioning pituitary adenoma"[all fields] OR "nonfunctioning pituitary adenomas"[all fields] OR "nonfunctioning pituitary macroadenoma"[all fields] OR "nonfunctioning pituitary macroadenomas"[all fields] OR "nonfunctioning macroadenoma"[all fields] OR "nonfunctioning macroadenomas"[all fields]) AND ("quality of life"[mesh] OR "quality of life"[all fields] OR "life quality"[all fields] OR "qol"[all fields] OR "daily functioning"[all fields] OR "daily routine"[all fields] OR "health related quality of life"[all fields] OR "well-being"[all fields] OR "wellbeing"[all fields])

PsycINFO:

("Pituitary Neoplasms" OR "Pituitary Neoplasms" OR "Pituitary Neoplasm" OR "Pituitary Tumors" OR "Pituitary Tumor" OR "Pituitary Adenomas" OR "Pituitary Adenomas" OR "ACTH-Secreting Pituitary Adenoma" OR "ACTH-Secreting Pituitary Adenomas" OR "Pituitary Corticotropin-Secreting Adenoma" OR "Pituitary Corticotropin-Secreting Adenomas" OR "Corticotroph Adenoma" OR "Corticotroph Adenomas" OR "Growth Hormone-Secreting Pituitary Adenoma" OR "Growth Hormone-Secreting Pituitary Adenomas" OR "Pituitary Growth Hormone Secreting Adenoma" OR "Pituitary Growth Hormone Secreting Adenomas" OR "Prolactinoma" OR "Prolactinomas" OR "Microprolactinoma" OR "Microprolactinomas" OR "Macroprolactinoma" OR "Macroprolactinomas" OR "Acromegaly" OR "non-functioning adenoma" OR "non-functioning adenomas" OR "non-functioning macroadenoma" OR "non-functioning macroadenomas" OR "nonfunctioning adenoma" OR "nonfunctioning adenomas" OR "nonfunctioning pituitary adenoma" OR "nonfunctioning pituitary adenomas" OR "nonfunctioning pituitary macroadenoma" OR "nonfunctioning pituitary macroadenomas" OR "nonfunctioning macroadenoma" OR "nonfunctioning macroadenomas" OR "Cushing syndrome" OR "Cushing syndrome" OR "Cushing's Syndrome" OR "Hypercortisolism" OR "Cushing disease" OR "Cushing's disease" OR "Cushings Syndrome" OR "Hypothalamic Pituitary Adrenal Axis" OR "Hypopituitarism" OR "Pituitary Disorders" OR "Hypopituitarism") AND ("Quality of Life" OR "Quality of Work Life" OR "Relationship Quality" OR "Family Relations" OR "Life Changes" OR "Life Experiences" OR "Lifestyle" OR "Spirituality" OR "quality of life" OR "quality of life" OR "life quality" OR "qol" OR "daily functioning" OR "daily routine" OR "limitations of functioning" OR "health related quality of life" OR "quality of life" OR "quality of life" OR "life quality" OR "qol" OR "daily functioning" OR "daily routine" OR "limitations of functioning" OR "health related quality of life" OR "well-being" OR "wellbeing")

Web of Science:

TS=(Pituitary Neoplasms OR Pituitary Neoplasm OR Pituitary Tumors OR Pituitary Tumor OR Pituitary Adenomas OR Pituitary Adenomas OR ACTH-Secreting Pituitary Adenoma OR ACTH-Secreting Pituitary Adenomas OR Corticotroph Adenoma OR Corticotroph Adenomas OR Cushing syndrome OR Cushing syndrome OR Cushing's Syndrome OR Hypercortisolism OR Cushing disease OR Cushing's disease OR Growth Hormone-Secreting Pituitary Adenoma OR Growth Hormone-Secreting Pituitary Adenomas OR Prolactinoma OR Prolactinomas OR Microprolactinoma OR Microprolactinomas OR Macroprolactinoma

OR Macroprolactinomas OR Acromegaly OR non-functioning adenoma OR non-functioning adenomas OR non-functioning macroadenoma OR non-functioning macroadenomas OR nonfunctioning adenoma OR nonfunctioning adenomas OR nonfunctioning pituitary adenoma OR nonfunctioning pituitary adenomas OR nonfunctioning pituitary macroadenoma OR nonfunctioning pituitary macroadenomas OR nonfunctioning macroadenoma OR nonfunctioning macroadenomas OR Cushing syndrome OR Cushing syndrome OR Cushing's Syndrome OR Hypercortisolism OR Cushing disease OR Cushing's disease) AND TS=(quality of life OR quality of life OR life quality OR qol OR daily functioning OR daily routine OR health related quality of life OR well-being OR wellbeing)

Embase:

(exp hypophysis tumor/ OR "Pituitary Neoplasms".mp OR "Pituitary Neoplasm".mp OR "Pituitary Tumors".mp OR "Pituitary Tumor".mp OR "Pituitary Adenomas".mp OR "Pituitary Adenomas".mp OR "ACTH-Secreting Pituitary Adenoma".mp OR "ACTH-Secreting Pituitary Adenomas".mp OR "Corticotroph Adenoma".mp OR "Corticotroph Adenomas".mp OR Cushing syndrome/ OR "Cushing syndrome".mp OR "Cushing's Syndrome".mp OR "Hypercortisolism".mp OR "Cushing disease".mp OR "Cushing's disease".mp OR "Growth Hormone-Secreting Pituitary Adenoma".mp OR "Growth Hormone-Secreting Pituitary Adenomas".mp OR "Acromegaly".mp OR "Prolactinoma".mp OR "Prolactinomas".mp OR "Microprolactinoma".mp OR "Microprolactinomas".mp OR "Macroprolactinoma".mp OR "Macroprolactinomas".mp OR "non-functioning adenoma".mp OR "non-functioning adenomas".mp OR "non-functioning pituitary adenoma".mp OR "non-functioning pituitary adenomas".mp OR "non-functioning macroadenoma".mp OR "non-functioning macroadenomas".mp OR "nonfunctioning adenoma".mp OR "nonfunctioning adenomas".mp OR "nonfunctioning pituitary adenoma".mp OR "nonfunctioning pituitary adenomas".mp OR "nonfunctioning pituitary macroadenoma".mp OR "nonfunctioning pituitary macroadenomas".mp OR "nonfunctioning macroadenoma".mp OR "nonfunctioning macroadenomas".mp) AND (exp "quality of life"/ OR "quality of life".mp OR "life quality".mp OR "qol".mp OR "daily functioning".mp OR "daily routine".mp OR "health related quality of life".mp OR "well-being".mp OR "wellbeing".mp)

APPENDIX 2. SPIDER PLOT DATA

PF: Physical functioning, PR: Physical role, GH: General health, Vit: Vitality, SF: Social functioning, ER: Emotional role, MH: Mental health

Dutch a-select sample (67)

	PF	PR	Pain	GH	Vit	SF	ER	MH
Average score	**81.9**	**79.4**	**79.5**	**72.7**	**67.4**	**86.9**	**84.1**	**76.8**

Prolactinoma

Active/naïve patient groups:

	PF	PR	Pain	GH	Vit	SF	ER	MH
Johnson, 2003	49.3	46.2	47.9	47	43.8	41.3	40.3	43.8
Average score	**49.3**	**46.2**	**47.9**	**47**	**43.8**	**41.3**	**40.3**	**43.8**

Controlled/treated patient groups:

	PF	PR	Pain	GH	Vit	SF	ER	MH
Cesar de Oliveira Naliato, 2008	78.6	86	70.1	69	61.1	69.5	67.3	66.6
Kars, 2007	85.5	70.9	81.2	67.6		73.4	75.8	
Average score	**82.1**	**78.5**	**75.7**	**68.3**	**61.1**	**71.5**	**71.6**	**66.6**

NFA

Active/naïve patient groups:

	PF	PR	Pain	GH	Vit	SF	ER	MH
Johnson, 2003	45.9	43	46.2	46.4	40.9	41.7	41.2	44.8
Average score	**45.9**	**43**	**46.2**	**46.4**	**40.9**	**41.7**	**41.2**	**44.8**

Controlled/treated patient groups:

	PF	PR	Pain	GH	Vit	SF	ER	MH
Biermasz, 2011 (remission)	85.6	76.5	87.8	68.4		89.0	90.2	
Dekkers, 2006 (remission)	79.0	65	81.3	57.3		79.0	69.1	
Page, 1997 (treated)	79	73	80	66	57	86	78	75
Nielsen. 2007 (treated)	84	72.4	82.8	70.1	66.3	90.6	77.5	82.3
Van Beek, 2007 (RT+)	84	76	84	60	66	85	88	79
Van Beek, 2007 (RT-)	74	69	81	59	56	77	78	72
Capatina, 2013 (treated)	71.5	64.5	75.3	62.1	55.0	79.1	75.9	76.6
Miller, 2008 (after GH therapy)	85.4	98.1	78.1	76.8	61.5	96.2	92.3	85.2
Miller, 2008 (after placebo)	63.9	62.5	61.1	48.6	46.1	67	57.1	66.3
Average score	**78.5**	**73.0**	**79.0**	**63.1**	**58.3**	**83.2**	**78.5**	**76.6**

Acromegaly

Active/naïve patients:

	PF	PR	Pain	GH	Vit	SF	ER	MH
Milian, 2013 (preoperative)	37	45.4	29.7	31.5	25.8	30.8	48.1	34.2
Johnson, 2003 (active)	46	45	46.5	43.6	43.5	46.7	47.1	47.2
Psaras, 2011 (no remission)	51	43.2	35.7	39.9	33.8	43.4	39.7	38.2
Average score	**44.7**	**44.5**	**37.3**	**38.3**	**34.4**	**40.3**	**45.0**	**39.9**

Controlled/treated patient groups:

	PF	PR	Pain	GH	Vit	SF	ER	MH
Miller, 2010 (after GH therapy)	85.4	98.1	78.1	76.8	61.5	96.2	92.3	85.2
Miller, 2010 (after placebo)	63.9	62.5	61.1	48.6	46.1	67	57.1	66.3
Wassenaar, 2010 (spine OA)	72.6	58.9	67.1	54.4		77.2	62	
Wassenaar, 2010 (no spine OA)	84.7	90	86.9	72.7		93.3	95.5	
Van der Klaauw, 2008 (follow-up)	72.1	67.4	72.6	59.9		79	75.1	
Wexler, 2009 (GHD)	72	68	64.9	55.2	38.4	74.5	72	66.7
Wexler, 2009 (GH sufficient)	94.4	100	84.6	78.3	66.8	95.8	100	78.2
Biermasz, 2004 (remission)	68.6	57.4	72.2	55.6		79.6	70.3	
Biermasz, 2005 (no joint problems)	83.9	76.9	92	70.6		88	84	
Biermasz, 2005 (joint problems)	64	51.7	66.3	51.2		77.1	66.3	
Postma, 2012 (SSTA+)	65	46	65	49	48	66	78	72
Postma, 2012 (SSTA-)	79	65	78	63	58	75	75	75
Milian, 2013 (12 months after surgery)	51.1	54.3	36.5	46.7	52.2	55.8	56.7	60.5
Miller, 2008 (controlled)	65	65.7	60.7	55.4	51	76.9	76.6	73
Psaras, 2011 (remission)	34.3	35.9	32.3	33.5	32.5	37.6	38.7	45.2
Valassi, 2012 (placebo)	63.8	68.8	63.1	38.8	26.9	65.6	62.5	55
Valassi, 2012 (GH)	80.6	58.3	76.4	61.7	28.9	70.8	77.8	65.3
Average score	**70.6**	**66.2**	**68.1**	**57.1**	**46.4**	**75.0**	**72.9**	**67.5**

Cushing's disease

Active/naïve patient groups:

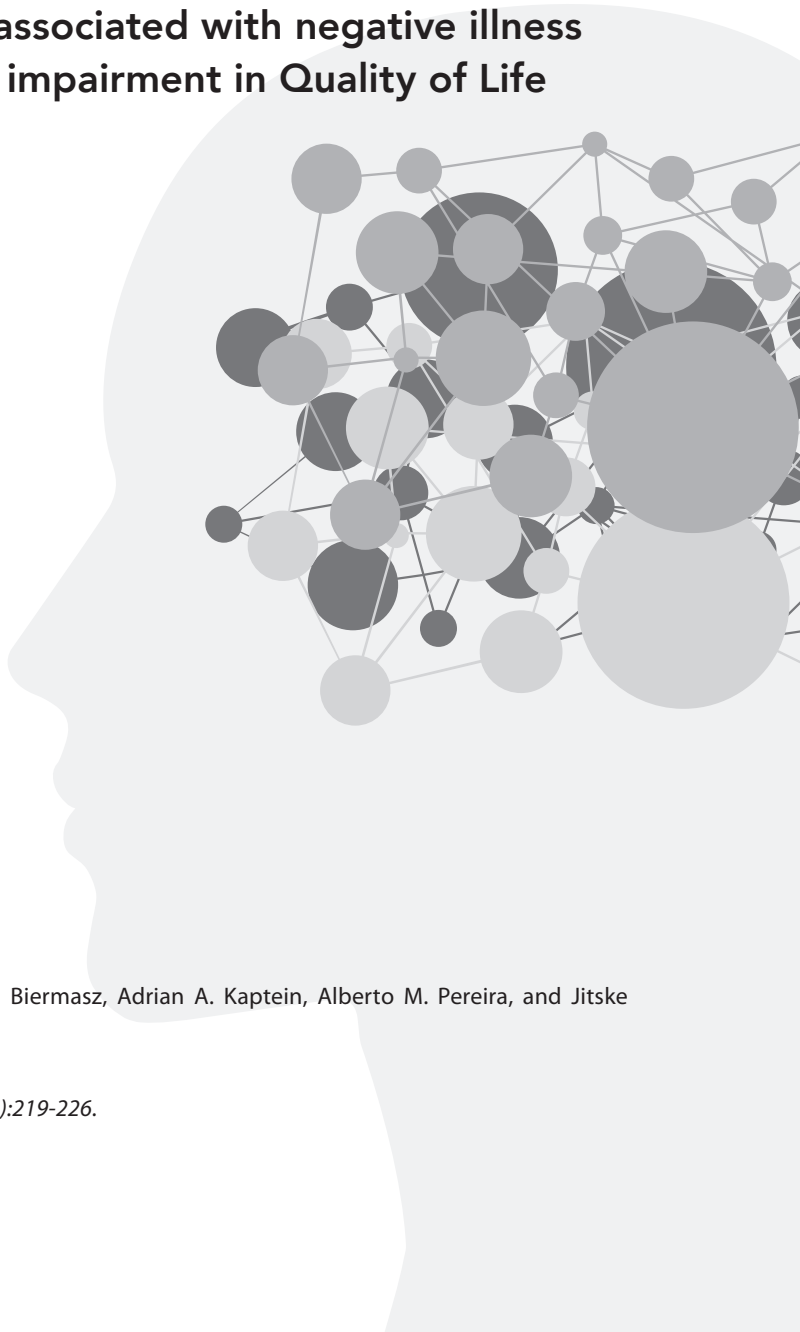
	PF	PR	Pain	GH	Vit	SF	ER	MH
Milian, 2013 (preoperative)	9.6	21.6	24.9	12.1	9.8	12.4	22.1	13
Johnson, 2003 (active)	36.6	36.1	40.8	36.4	35.4	35	38.8	38.4
Psaras, 2011 (no remission)	37.6	25	44.6	39.7	47.2	31.6	26	43.8
Lindsay, 2006 (pre-surgery)	28.3	31.8	41.9	34.4	36.4	29.8	36.6	39.7
Van der Pas, 2012, 2013 (untreated)	54.4	33.6	75.3	45.6		59.4	60.4	
Average score	**33.3**	**29.6**	**45.5**	**33.6**	**32.2**	**33.6**	**36.8**	**33.7**

Controlled/treated patient groups:

	PF	PR	Pain	GH	Vit	SF	ER	MH
Lindsay, 2006 (remission)	45.5	45.7	47.4	44.2	46.5	47.2	45.6	47.3
Lindsay, 2006 (after surgery)	45.9	45.9	48.6	48.1	48.3	46.7	49	51.4
Van Aken, 2005 (remission)	68	65	73	54		73	67	
Tiemensma, 2012 (remission)	63.5	51.3	69.6	50.1	48.6	72.1	62.7	61.4
Milian, 2013 (12 months after surgery)	41.9	39.5	43	37.5	32	40.5	42.9	52.1
Psaras, 2011 (remission)	43.3	40.1	38.3	31.6	36.9	32.9	58.3	40.7
Hawn, 2012 (after adrenalectomy)	65	39	52	44	30	53	43	58
Smith, 2009 (after adrenalectomy)	48.5	45.4	50.1	42.5	41.8	45.1	48.9	46.6
Average score	**52.7**	**46.5**	**52.8**	**44.0**	**40.6**	**51.3**	**52.2**	**51.1**

CHAPTER 10

More concerns and stronger beliefs about the necessity of medication in patients with acromegaly are associated with negative illness perceptions and impairment in Quality of Life



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ABSTRACT

Objective: Patients with acromegaly can be treated with surgery, radiotherapy and/or medical treatment. In general, patients' beliefs about medication are associated with illness perceptions, a contributory factor of Quality of Life (QoL). At present, there are no quantitative studies on medication beliefs in patients with acromegaly. Here, we aimed to examine possible associations between medication beliefs, illness perceptions, and QoL. Furthermore we aimed to explore whether illness perceptions of patients with remission of acromegaly receiving medical treatment differ from patients without medical treatment.

Design: Cross-sectional evaluation of 73 patients with remission of acromegaly (n=28 patients with medication, n=45 without medication). The Beliefs about Medicines Questionnaire (BMQ), Illness Perception Questionnaire-Revised (IPQ-R), EuroQoL-5D, and AcroQoL were used for the assessment.

Results: Stronger beliefs about the necessity of medical treatment and stronger concerns about the adverse effects were associated with attributing more symptoms to acromegaly, perceiving more negative consequences, and having a stronger belief in a cyclical timeline (BMQ, all $P<0.05$). Stronger beliefs about the necessity of medical treatment were associated with a worse disease-specific QoL (BMQ, $P<0.01$). Patients with medical treatment perceived a more chronic timeline of their disease, compared to patients without medical treatment (IPQ-R, $P=0.002$).

Conclusion: Negative medication beliefs were related to more negative illness perceptions and worse disease-specific QoL. Patients receiving medical treatment for acromegaly tend to perceive a more chronic timeline of their disease, compared to patients with remission without medical treatment. These psychological factors need to be taken into account when treating patients and developing a psychosocial education program aiming to improve QoL.

INTRODUCTION

Acromegaly is characterized by exposure to elevated growth hormone (GH) levels, most frequently due to a GH-producing pituitary adenoma. Patients are usually treated with transsphenoidal surgery and sometimes by additional radiotherapy. When this treatment is not (completely) successful, or when surgery and/or radiotherapy is not preferred, patients can be medically treated with somatostatin analogs (SA) (e.g. Octreotide, Lanreotide) and/or a GH receptor antagonist (e.g. Pegvisomant). Patients with acromegaly report impairments in Quality of Life (QoL) (1;2), which may persist even after long-term remission (3;4). These persistent impairments have been (partly) attributed to comorbidities, such as osteoarthritis (5), musculoskeletal pain (6-8), and psychopathology (9). Besides physical factors, Tiemensma et al. elucidated psychological factors (i.e. negative illness perceptions) which were related to QoL impairments in patients after long-term remission of acromegaly (10).

Recently Gurel et al. carried out structured interviews that explored patients' perceived impact of acromegaly. These interviews revealed that patients did not feel "cured" after treatment, particularly when patients realized they had to take medication for the rest of their life. The use of medication resulted in confusion between being a patient and being a person. Furthermore, patients had to make specific injection schedules to plan their medication around work, travel, and big events, in order to minimize the negative influence of side-effects on everyday life (11). A previous focus group study carried out by our group elucidated medicine beliefs and illness perceptions in patients with acromegaly. Specifically, during these focus group conversations patients reported that they experienced the use of injections as awful (12) (for illustrative, unpublished quotes, see Table 1). These two qualitative studies point toward the potential existence of negative beliefs about medicines in patients medically treated for acromegaly. Furthermore, it illustrated the need for self-management skills in patients with acromegaly in order to minimize the negative influence on their daily life.

Beliefs about medicines can be quantitatively assessed by using the Beliefs about Medicines Questionnaire (BMQ) (13), which assesses beliefs about necessity and concerns of taking a specific medicine. Until now, there are no quantitative studies available about beliefs about medication for acromegaly (i.e. SA) and beliefs about medication in general in patients with acromegaly.

The important influence of beliefs about medicines on illness perceptions, coping strategies, and therefore QoL, is demonstrated in the Common-Sense Model of self-regulation (CSM) (14). This model describes how individuals come to understand their illness and how they develop coping strategies. The model comprises three stages. During stage one, illness perceptions are identified and organized around five categories: identity, cause, timeline, consequences, and cure/control. These illness perceptions determine coping strategies (stage two). The third stage comprises the appraisal of these coping strategies. Recently, the extended CSM was formulated by including beliefs about medicines. Specifically, it was demonstrated that beliefs about medicines were associated with illness perceptions in pa-

tients with chronic diseases (e.g. asthma (15)), adrenal insufficiency (16)). In addition, beliefs about medicines have also been found to be predictive of self-management behavior, such as adherence to medication (15;17).

Table 1. Illustrative quotes on medication beliefs and illness perceptions in acromegaly

Medicine beliefs: concerns	*I take very intense medications, which is difficult.*
	I noticed, towards the end of my injections, that my sleep problems increased. My body would start functioning differently when my injection would wear off.
	I find information about side effects very important. I thought those side effects were very severe.
Illness perception: Identity	*I believe I am just tired earlier and experience stress faster.*
	You are more sensitive to stress, which has an impact on your physical well-being, I think.
	Your central nervous system must be damaged here and there because of the illness, it is almost inevitable.
Illness perception: Consequences	*It had a huge impact. You are working, you have a house, you have a good job, and all of a sudden you are ill.*
	In the meantime, you basically lost your entire life.
	It is very two-sided of course. On the one hand, you are happy to know where your symptoms came from after getting the diagnosis. Subsequently, you undergo surgery, which goes well, and afterwards you are happy you are still alive, you can finally do all the fun things you haven't done in years, because I was always working and very busy. Afterwards, you still have a body that doesn't want to even though you want it to. That is difficult sometimes.
Illness perception: Timeline	*You feel like you may have been cured because the values normalized so the surgery was successful, but the damage that preceded this is permanent so you obviously have damage somewhere.*
	Permanent damage, that troubles me the most.
	You may not actually be sick, but you do have a disease as a result.
	And you keep that with you for the rest of your life, so to what extent are you cured?

Unpublished quotes from a recent focus group study of our department. The main results are described in (12). During the focus groups patients with acromegaly reported concerns about their medication, and perceptions about the identity of their disease, the consequences and the timeline.

In the present study, we aimed to assess the contribution of beliefs about medicines to illness perceptions and QoL in acromegaly. We examined possible associations between beliefs about medication, illness perceptions, and QoL in patients with remission of acromegaly. Considering the extended CSM we hypothesized that beliefs about medication are associated with illness perceptions and QoL. Furthermore, we evaluated whether there are differences in illness perceptions and QoL between patients with remission of acromegaly

receiving medical treatment and patients without medical treatment. Considering the potential negative effect patients may perceive when taking medication for acromegaly (11;12), we hypothesized that patients medically treated for acromegaly have more negative illness perceptions and more impairments in QoL compared to patients in remission without medical treatment.

PATIENTS AND METHODS

Design

Patients with acromegaly were invited to fill out questionnaires on medication beliefs, illness perceptions, and QoL. Patients were asked to complete the questionnaires at home and return them in a prepaid envelope. Inclusion criteria were adult patients (age >18yr) and remission defined by strict biochemical criteria (see below for details) for at least 1 year. Institutional Medical Ethics Committee approved the protocol.

Patients

A clinical chart review of 156 patients with acromegaly was performed. All patients were in biochemical remission for at least 1 year at the time of the present study. We invited these patients to fill out the questionnaires. Seventy-three patients (47%) refused to participate for several reasons (e.g. too busy, old age, debilitating disease). Eighty-three (53%) patients returned the questionnaires and filled out at least one questionnaire. Seventy-seven of these patients (49%) completed both the *Beliefs about Medicines Questionnaire,* as well as the *Illness Perception Questionnaire*. Patients with acromegaly who used medication other than somatostatin analogs (SA), i.e. dopamine agonists (n=2), or Pegvisomant (n=2) were excluded from the analysis because of the low power for separate analyses. Therefore, a final number of 73 patients (47%) were included in the present study. Sixty-five of these patients (42%) also filled out QoL questionnaires. For an overview of this process, see Figure 1.

The diagnosis of acromegaly had been established by clinical signs and symptoms, and by biochemical tests, including insufficient suppression of GH during the glucose tolerance test and increased IGH-I levels for age. Normal serum IGF-I levels for age and serum GH levels below 1.9 µg/liter defined biochemical control of acromegaly for all patients and, in patients without SA treatment, also by suppression of GH levels (<0.38 mcg/l) during glucose tolerance test (18). Remission was reconfirmed at yearly intervals. Pituitary function was monitored and pituitary hormone replacement was prescribed dependent on the results of the yearly evaluation of pituitary functions. In case of corticotrope insufficiency, documented by insulin tolerance test (ITT) or CRH test, hydrocortisone was prescribed (20 mg/d divided into 2-3 dosages). Evaluation of GH deficiency was performed by ITT or GHRH-arginine test, only in patients under the age of 70 years and only after at least 2 years of remission. Somato-

trope insufficiency was treated with rhGH replacement, aiming at IGF-I concentrations in the normal range for age. In addition, free T4 and testosterone levels (in male patients) were assessed. If results were below the lower limit of the respective ranges, substitution with L-T4 and/or testosterone was prescribed. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was provided.

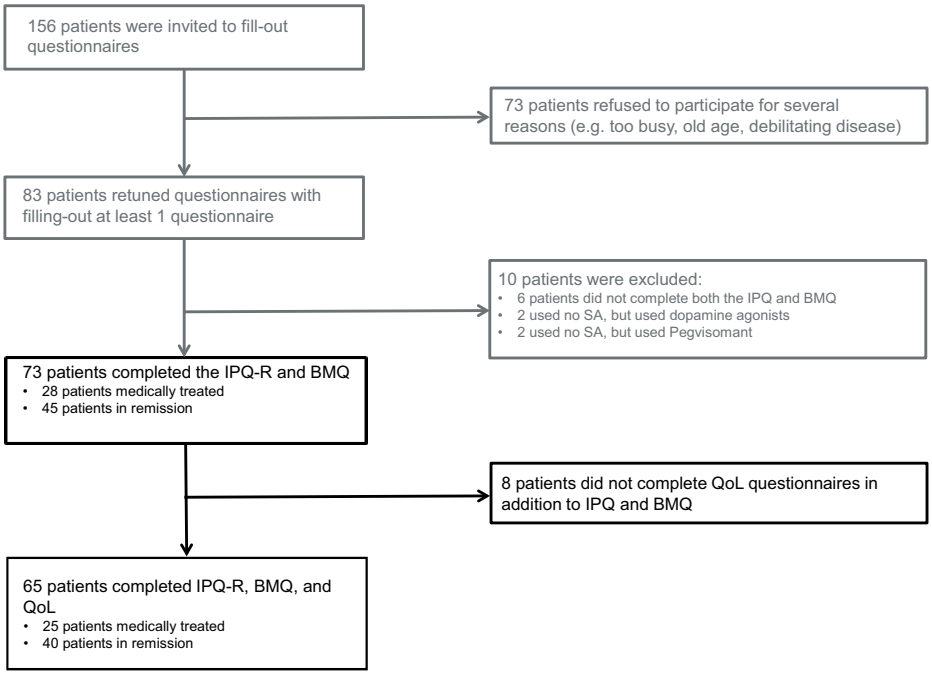

Figure 1. Flow-chart of included patients.

Questionnaires

Beliefs about Medicines Questionnaire (BMQ)

The BMQ aims to assess cognitive and emotional representations of medication and comprises of two sections (i.e. BMQ-Specific and BMQ-General), each divided into two subscales. The BMQ-Specific comprises two subscales assessing representations of medication prescribed for personal use (i.e. SA): the *Specific-Necessity* subscale, which is focusing on the perceived necessity of taking medications to remain healthy, and the *Specific-Concerns* subscale, focusing on concerns about the adverse effects of taking medications. The BMQ-General comprises two four item subscales assessing beliefs about medicines in general: the *General-Overuse* subscale assesses beliefs that medicines are over-prescribed, and the *General-Harm* subscale assesses beliefs about medicines as harmful, addictive or poisonous. All items were

rated on a five-point Likert-scale ranging from 1 strongly agree to 5 strongly disagree. The Specific-Necessity subscale ranged from 5 to 25 (midpoint = 15), the Specific-Concerns subscale ranged from 6-30 (midpoint = 18), and both General subscales ranged from 4 to 20. Higher scores indicate stronger beliefs. Among general medical patients, the Cronbach's alpha ranged from 0.51 to 0.86 (13).

Illness Perception Questionnaire - Revised (IPQ-R)

The Illness Perception Questionnaire-Revised (IPQ-R) was used to assess cognitive and emotional representations of illness. The questionnaire was developed to assess the components of the illness representation of Leventhal's Common Sense Model and is frequently used to study illness perceptions in chronic conditions (19-23). The IPQ-R is divided into three sections. The first part consists of the illness identity dimension, with a list of fourteen general commonly occurring symptoms. Patients are asked to rate whether or not they experienced the symptoms, and if they believe the symptom to be related to their illness (yes/no). The summed yes-rated items of the disease related symptoms are used in the analysis.

The second part of the questionnaire, assessing illness perception dimensions, consists of 38 statements concerning views on the illness, scored on a 5-point Likert scale (from strongly disagree to strongly agree). The questions are transformed to seven dimensions: timeline acute/chronic (beliefs about the chronic nature of the condition), timeline cyclical (beliefs regarding the cyclical nature of the condition i.e. perceived variability in symptoms), consequences (negative consequences of the disease), personal control (perceived personal controllability of the disease), treatment control (perceived treatment controllability of the disease), emotional representations (the emotional responses generated by the illness), and illness coherence (personal understanding of the disease). A higher score indicates a stronger belief in that particular dimension. The third and final part of the questionnaire is about the causal attributions. This section consists of 18 statements concerning possible causes that patients consider that contributed to their disease, scored on a 5-point Likert scale (strongly disagree to strongly agree).

As recommended by the developers of the questionnaire, a principal component analysis with varimax rotation was performed on the causal items to cluster variables with shared variance (24). This analysis produced two factors: 1) psychological attributions (i.e. stress/worries, family problems/worries, emotional state, mental attitude, own behavior, overwork, aging, personality, altered immunity, poor medical care), and 2) risk factors (smoking, alcohol use, accident/injury, bacteria/virus, diet/eating habits, pollution in environment). The principal component analysis is described in detail by Tiemensma et al. 2010 (10).

EuroQoL-5D (EQ-5D)

The EQ-5D assesses the current health status reflected in five health dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores are expressed

on a 1-3 scale per dimension, with higher scores indicating worse QoL. The questionnaire also includes a visual analogue scale (VAS) which comprises a standard vertical 20 cm scale (similar to a thermometer) for recording an individual's rating for their current health-related well-being (25). The VAS score ranges from 0 to 100, with higher scores indicating a better health status.

AcroQoL

The AcroQoL is a disease-specific QoL questionnaire assessing acromegaly related QoL. The AcroQOL consists of 22 items on a five-point Likert scale, measuring frequency of occurrence (ranging from always to never) and agreement (ranging from completely agree to completely disagree). The 22 items are subdivided into three subscales: physical scale (8 items), psychological-appearance scale (7 items), and psychological-personal relations scale (7 items). The total score ranges from 0-100, with lower scores indicating a more impaired QoL (26;27).

Statistical analysis

Data were analyzed using PASW Statistics version 20 (SPSS Inc., Chicago, IL). All data are presented as means ± standard deviations, unless mentioned otherwise. To check the normality of data, the Kolmogorov-Smirnov test was used in addition to histograms and boxplots.

The primary analysis comprised the relationship between medication beliefs, illness perceptions and QoL. Pearson correlation coefficients were calculated when data were normally distributed and Spearman's rho were calculated when data were not normally distributed. The secondary analysis comprised the evaluation of potential differences in illness perceptions between patients with medical treatment for acromegaly and patients without medical treatment. Independent sample t-tests were used when data were normally distributed and Mann-Whitney U tests were used when data were not normally distributed. Because of the exploratory nature of the primary and secondary analysis, adjustment of the level of significance for multiple testing was not performed, and the level of significance was set at $P \leq 0.05$.

RESULTS

Patient characteristics (Table 2)

Seventy-three patients participated in the present study (40 males, 55%). The mean duration of follow-up was 16.1±10 years. Eighty-five percent of the patients were treated with transsphenoidal surgery, and 23% of the patients were additionally treated with radiotherapy. Forty-five patients were not using medication for acromegaly. Of these patients, 44 patients (98%) were treated with transsphenoidal surgery and one patient was biochemically cured after pituitary apoplexy. Twenty-eight patients were receiving medical treatment for acromegaly. Of these medically treated patients, 18 patients (25%) used only SA, six patients

(8%) used SA and Pegvisomant, three patients (4%) used SA and dopamine agonists, and one patient used SA, Pegvisomant, and dopamine agonists. Patients only using Pegvisomant (n=2) or dopamine agonist (n=2) had been excluded from the analysis. All medically treated patients were well-controlled as measured by GH (in SA patients only) and IGF-1 concentrations (in all 28 patients) that were below 2.5 mcg/L and within the normal reference range, respectively (biochemical remission).

Of the SA treated, 79 percent reported the need for using SA (scores above the midpoint of the specific necessity subscale), whereas 50 percent of these patients reported concerns about the use of SA (scores above the midpoint of the specific concerns subscale).

Table 2. Patient characteristics

	All patients (N=73)	**Patients medically treated for acromegaly (n=28)**	**Patients without medical treatment for acromegaly (n=45)**	**P-value[a]**
Gender (male/female)	40/33	13/15	27/18	.257[c]
Age (yrs)	60.10 (11.6)	59.96 (11.0)	60.18 (12.1)	.860[b]
Education (n)				.403[c]
Low	29 (40%)	9 (32%)	20 (44%)	
Medium	17 (23%)	6 (22%)	11 (25%)	
High	27 (37%)	13 (46%)	14 (31%)	
Transsphenoidal surgery, n (%)	62 (85%)	18 (64%)	44 (98%)	.000[c]
Additional radiotherapy, n (%)	17 (23%)	5 (18%)	12 (27%)	.387[c]
Somatostatin analogs only	18 (25%)	18 (64%)	NA	NA
Somatostatin analogs & Pegvisomant	6 (8%)	6 (21%)	NA	NA
Somatostatin analogs & Dopamine agonists	3 (4%)	3 (11%)	NA	NA
Somatostatin analogs & Pegvisomant & Dopamine agonists	1 (1%)	1 (4%)	NA	NA
Duration follow-up (yrs)	16.07 (10.0)	13.96 (10.8)	17.38 (9.4)	.067[b]
Hypopituitarism, n (%)				
GH	12 (16%)	0 (0%)	12 (27%)	.003[c]
LH/FSH	13 (18%)	5 (18%)	8 (18%)	.993[c]
TSH	19 (26%)	6 (21%)	13 (29%)	.480[c]
ACTH	19 (26%)	5 (18%)	14 (31%)	.210[c]
ADH	2 (3%)	0 (0%)	2 (4%)	.258[c]

[a] patients medically treated for acromegaly (n=28) vs. patients without medical treatment for acromegaly (n=45), [b] Mann-Whitney U test, [c] Chi-Square test.

Relationship between medicines beliefs and illness perceptions (Table 3, Figure 2)

In the subgroup of patients using SA, *Specific-Necessity* SA (i.e. the necessity of taking SA to remain healthy) was positively associated with illness identity (r=.406, P=.032) and consequences (r=.398, P=.040). This indicates that stronger beliefs about the necessity of SA to stay healthy are related to attributing more symptoms to acromegaly and perceiving more nega-

Table 3. Correlations between illness perception dimensions, EQ-5D dimensions, BMQ dimensions, and disease-specific quality of life

	Specific Necessity (SA) (n=28)[a]	Specific Concerns (SA) (n=28)[a]	General Harm (n=73)[b]	General overuse (n=73)[b]
IPQ-R				
Identity	.406*	.367	.053	-.040
Timeline (chronic/acute)	.173	-.278	-.186	-.202
Timeline (cyclical)	.266	.396*	-.020	.066
Consequences	.398*	.348	.009	-.040
Emotional representations	.290	.294	.280*	.269*
Personal control†	.012	-.076	.141	.139
Treatment control	-.331	-.298	-.108	-.109
Illness coherence	-.069	-.277	.007	-.002
Psychological attributions	-.059	.144	.237*	.176
Risk factors	-.050	.253	.240*	.157
	Specific Necessity (SA) (n=25)[c]	**Specific Concerns (SA) (n=25)[c]**	**General Harm (n=65)[d]**	**General Overuse (n=65)[d]**
EQ-5D				
Mobility	.265	.034	-.031	.025
Self-care	.206	.155	.117	.132
Activity	.275	.099	.017	.060
Pain	.140	.262	-.011	-.018
Anxiety	-.144	.203	-.073	-.022
VAS†	-.361	-.281	-.164	-.112
AcroQoL				
Physical scale	-.383	-.184	.010	-.002
Psychological-appearance†	-.423*	.034	.163	.054
Psychological-personal relations†	-.567**	-.311	.029	-.007
Total score†	-.594**	-.006	.078	.025

Spearman's correlations; † Pearson's correlations. *P<0.05, **P<0.01; [a]= patients medically treated for acromegaly who filled out IPQ-R and BMQ. [b]= total sample of patients with and without medication for acromegaly who filled out IPQ-R and BMQ. [c]= patients medically treated for acromegaly who filled out AcroQoL and EQ-5D, as well as IPQ-R and BMQ. [d]= total sample of patients with and without medication for acromegaly who filled out AcroQoL and EQ-5D, as well as IPQ-R and BMQ. SA: somatostatin analogs.

tive consequences. *Specific-Concerns* SA (i.e. concerns about the adverse effects of taking SA) were positively associated with perceptions of a cyclic timeline (r=.396, P=.037), indicating that stronger concerns about the adverse effects of SA are related to perceiving a more cyclic timeline of the disease i.e. more perceived variability in symptoms.

In the entire sample, the subscale *General-Harm* (i.e. beliefs about medicines in general being harmful, addictive or poisonous) was positively associated with emotional representations (r=.280, P=.017), psychological attributions (r=.237, P=.048), and risk factors (r =.240, P =.045). This indicates that stronger beliefs about harm of medication use in general are related to stronger emotional responses generated by the disease, having stronger beliefs about psychological causes of the disease, and perceiving risk factors to be the cause of the disease. The subscale *General-Overuse* (i.e. beliefs that medicines in general are overprescribed) was also positively associated with emotional representations (r=.269, P=.022) indicating that stronger beliefs about the overuse of medication in general are related to having stronger emotional responses generated by the disease.

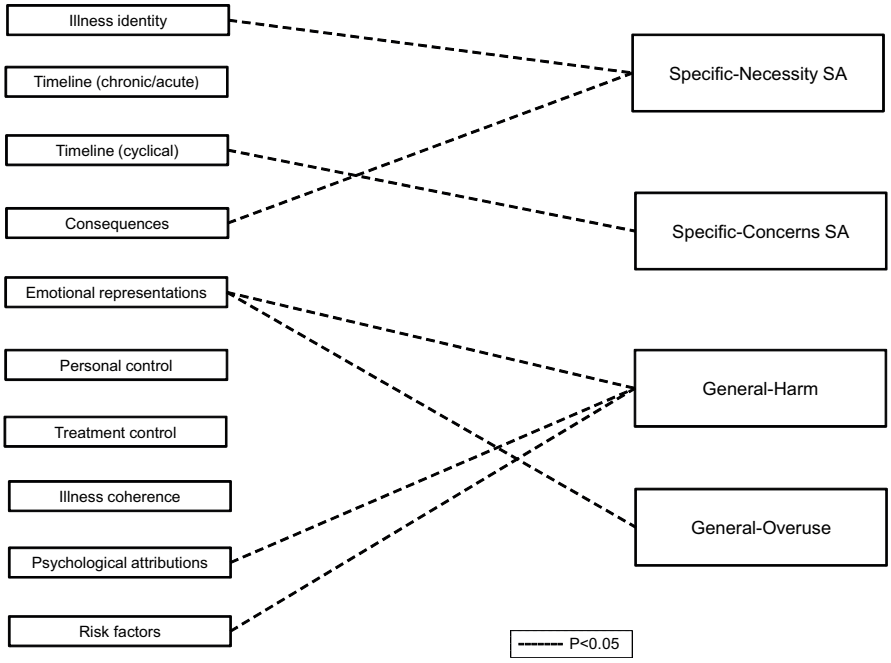

Figure 2. Observed correlations between illness perceptions and medication beliefs.
SA: somatostatin analogs. Absence of line indicates non-significant correlation.

Relationship between medicines beliefs and QoL (Table 3)

Specific-Necessity SA (i.e. the necessity of taking SA to remain healthy) was negatively associated with AcroQoL subscales Psychological-appearance (r=-.423, P=.035) and Psychological-personal relations (r=-.567, P=.009), and the total score on the AcroQoL (r=-.594, P=.007). This indicates that stronger beliefs about the necessity of SA to stay healthy are related to a worse disease-specific QoL.

The other specific, as well as general subscales of the BMQ were not significantly associated with QoL.

Illness perceptions and QoL in patients undergoing medical treatment vs. patients in remission (Table 4)

Patients treated with SA reported to perceive the timeline of their disease more chronically compared to patients in remission (25.69±4.07 versus 20.95±6.47, P=.002).

There were no significant differences on the other illness perception subscales or QoL scores between patients with medical treatment and patients without medical treatment.

DISCUSSION

The present study demonstrates that medication beliefs in patients with acromegaly are related to illness perceptions and QoL. Stronger beliefs about the necessity of SA 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 SA were associated with perceiving more variability in symptoms. Furthermore, patients who are medically treated for acromegaly with adequate biochemical control of disease have stronger beliefs about the chronicity of the disease than patients in remission without medical treatment for acromegaly.

The found correlations, together with the previously described correlations between illness perceptions and QoL in patients with acromegaly by Tiemensma et al. (10), support the theory of the extended CSM. This extended model shows how medication beliefs are associated both with illness perceptions and QoL in patients with chronic diseases (15;16).

Concerns about medication and negative illness perceptions in patients with acromegaly have been previously elucidated in a recent qualitative focus group study by our research group (12) (see Table 1). The present study provided quantitative data about these medication beliefs and illness perceptions. The important role of medication, and therefore of medication beliefs, is also properly illustrated by a recent interview study of Gurel et al. in which patients reported they felt not "cured" after treatment, particularly when they realized the medication had to be taken lifelong. The use of medication resulted in confusion between being a patient and being a person (11). The results of our study are in accordance with the latter study, since we demonstrate that patients using medication reported stronger beliefs

Table 4. Illness perceptions of patients with medication vs. patients in remission

	Patients medically treated (n=28)	Patients in remission (n=45)	P-value
IPQ-R			
Identity	2.86 (2.22)	2.31 (2.56)	.202
Timeline (chronic/acute)	25.69 (4.07)	20.95 (6.47)	.002*
Timeline (cyclical)	10.11 (4.14)	10.23 (3.80)	.788
Consequences	16.89 (5.44)	16.67 (5.11)	.898
Emotional representations	12.18 (3.20)	12.71 (3.73)	.361
Personal control†	17.06 (4.14)	17.44 (4.94)	.734
Treatment control	18.68 (3.03)	17.69 (3.51)	.299
Illness coherence	17.86 (2.81)	17.07 (2.69)	.137
Psychological attributions	16.18 (5.61)	19.26 (7.19)	.076
Risk factors	9.22 (3.33)	10.60 (3.74)	.161
BMQ			
Specific Necessity SA	17.04 (3.54)	NA	NA
Specific Concerns SA	17.75 (2.61)	NA	NA
General harm	9.69 (2.67)	9.71 (2.64)	.914
General overuse	10.13 (2.69)	10.77 (2.09)	.215
EQ-5D[a]			
Mobility	1.44 (0.51)	1.33 (0.47)	.354
Self-care	1.08 (0.28)	1.05 (0.22)	.627
Activity	1.56 (0.65)	1.52 (0.60)	.885
Pain	1.80 (0.65)	1.75 (0.59)	.787
Anxiety	1.28 (0.54)	1.42 (0.64)	.342
VAS†	69.58 (14.68)	69.77 (16.31)	.963
AcroQoL[a]			
Physical	64.32 (21.33)	61.14 (20.56)	.551
Psychological-appearance†	62.14 (22.14)	52.56 (18.84)	.069
Psychological-personal relations†	81.43 (11.45)	77.38 (14.56)	.289
Total score†	71.83 (15.50)	63.57 (14.09)	.052

Mann-Whitney U test; † Independent sample t-test. Data presented as mean (standard deviation). *P<0.01. [a] Patients medically treated for acromegaly (n=25) and Patients without medical treatment for acromegaly (n=40). SA: somatostatin analogs.

about the chronicity of the disease than patients not using medication. This negative illness perception about a more chronic time line of the disease may lead to more impairments in QoL, as demonstrated by Tiemensma et al. (10). This would be in accordance with previous literature demonstrating that patients with controlled acromegaly treated with Lanreotide reported worse QoL, compared with controlled patients who did not have to take medication (28), and patients cured by a single surgical intervention reporting better QoL than patients cured with SA, radiotherapy, or treated for hypopituitarism (3). However, in the present study

we did not find differences in QoL between patients medically treated and patients without medical treatment, which is in accordance with others (29;30), but which could also be due to limited power due to the relatively small sample size.

It might be that the association between medication beliefs and disease-specific QoL is mediated by the previously demonstrated relation between medication beliefs and self-management behavior (e.g. adherence to medication) (15), since adequate self-management skills are needed to optimize coping with the disease and it consequences, in order to minimize the negative influence on daily life (i.e. QoL). Future research in a larger group of medically treated patients with acromegaly is needed to further elucidate the role of medication beliefs in self-management behavior and QoL. Furthermore, it would be interesting to examine whether medication beliefs (and illness perceptions) can be modified by offering a psychosocial intervention, and whether changes towards more adaptive beliefs affect QoL. In addition, it should be acknowledged that illness perceptions and beliefs about treatment are related to cultural background (31-33). In the present study, ethnicity or cultural background was not assessed, and therefore analyses could not be adjusted for culture.

In a previous study by our research group in patients with adrenal insufficiency treated with hydrocortisone, we demonstrated strong and consistent correlations between beliefs about hydrocortisone and illness perceptions (16). The correlations found in the present study are similar to those in patients with adrenal insufficiency and demonstrated the same direction of correlations (i.e. stronger necessity beliefs and more concerns are related with more negative illness perceptions). However, in the present sample of patients medically treated for acromegaly, fewer correlations were found and correlations were less strong. This could possibly be explained by limited power due to a relatively small sample size. On the other hand, it could also be that the impact of medication in acromegaly is less strong compared to hydrocortisone treatment. Comparing the mean medicine beliefs about SA in the present sample with medicine beliefs in patients treated with hydrocortisone (i.e. necessity beliefs ranging from 18.4 to 20.9, and concerns ranging from 18.1 to 18.9 respectively) (16), it can be noted that medicine beliefs about SA are less strong. As suggested by the authors of the BMQ, differences between groups could be explained by differences in diagnosis, type of treatment, and perceived side effects (34). Therefore, we postulate that these distinctions could indeed be related to the different diagnoses, but also to the differences in type of treatment (i.e. suppressant medication vs. replacement therapy, injections vs. pills). Furthermore, there could be differences in perceived side effects (e.g. forgetting hydrocortisone intake could be life threatening, while forgetting SA is not).

The results of this study can be used by the treating physician during their consultations, but also by medical psychologists during psychological treatment. Awareness of clinicians about the potential existence of negative medication beliefs and/or illness perceptions would be helpful in order to assess those beliefs. Furthermore, an adequate assessment of these beliefs is needed to determine the potential strategy to adapt these beliefs in order

to improve self-management behavior, and therefore QoL. When needed, physicians could cooperate with medical psychologists and refer patients for psychological treatment, since a medical psychologist can assist patients to adapt inadequate cognitions in order to develop effective self-management strategies. This strategy is in accordance with the multi-phase approach described in a previous paper by our research group (16). This multi-phase approach consists of three phases: 1) provide patients with a clear rational for their medication, 2) assess and address patients' concerns regarding their medication use (when necessary in cooperation with a medical psychologist), and 3) support patients in the optimal and persistent use of their medication by assessing the potential barriers regarding their medication use. We believe that such a multi-phase approach that includes collaboration with a medical psychologist, enables improving medication beliefs, more positive illness perceptions, better self-management strategies, and thereby improving QoL.

In conclusion, specific beliefs about the necessity of somatostatin analogs and concerns about its adverse effects are strongly associated with more negative illness perceptions and worse disease-specific QoL. Furthermore, patients with remission of acromegaly who are medically treated perceive a more chronic timeline of their disease than patients in remission without medical treatment. The findings of the present study could be incorporated in routine clinical care of patients with acromegaly, enabling optimized clinical care, and are instrumental in the development of a self-management intervention aiming to improve QoL.

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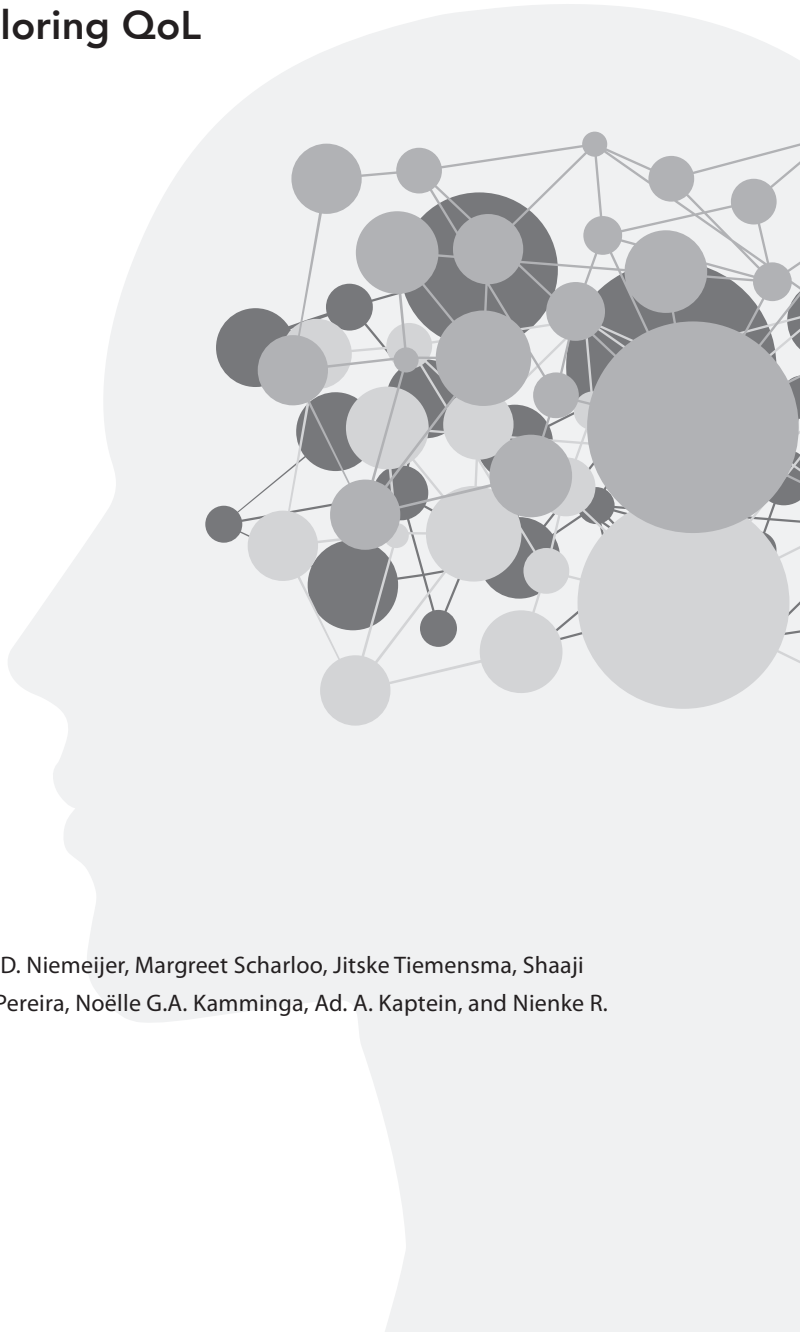
CHAPTER 11

Towards a better quality of life (QoL) for patients with pituitary diseases: Results from a focus group study exploring QoL



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ABSTRACT

Purpose: Patients treated for pituitary adenomas generally report a reduced quality of life (QoL). At present, the patient's perspective of QoL has not been fully addressed and this, and further insight in potential determinants of QoL in pituitary diseases is required to design strategies to improve QoL. We aimed to define patients' perceived QoL and to identify potential factors they perceive to contribute to QoL.

Methods: We conducted four independent focus groups of 6 patients each, per specific pituitary disease (Cushing's disease, Non-functioning pituitary macroadenoma, acromegaly, prolactinoma). In two sessions these focus groups discussed aspects of QoL. Verbatim transcripts were analyzed using a grounded theory approach.

Results: The issues raised by the patient groups were compatible with statements and items of available QoL questionnaires. In addition, other QoL aspects emerged, such as visual limitations (*physical problems*); 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 (*psychological problems*); and difficulties communicating about the disease, lack of sympathy and understanding by others, and a reduced social network (*social problems*). Next, this study uncovered factors which might contribute to a decreased QoL (e.g. less effective coping strategies, negative illness perceptions, negative beliefs about medicines, unmet needs regarding care).

Conclusions: This focus group study demonstrated that important disease-specific aspects of QoL are neglected in current pituitary disease-specific questionnaires and elucidated potential factors that contribute to a decreased QoL. Information provided in this study can (and will) be used for developing additional items for disease-specific QoL questionnaires and for the development of a self-management intervention aiming to improve QoL in patients treated for pituitary diseases.

INTRODUCTION

Patients with pituitary diseases experience considerable physical and psychosocial consequences in the chronic state of their disease (1). Persistently impaired quality of life (QoL) was observed in patients in biochemical remission of Cushing's disease (2-4), non-functioning macroadenoma (NFA) (4;5), acromegaly (4;6), and prolactinoma (4;7). QoL has been reported to improve after successful biochemical treatment, but does not normalize. QoL has been usually assessed by either generic questionnaires (e.g. Medical Outcome Study 36-item Short Form health survey, Nottingham Health Profile), dimension specific questionnaires (e.g. Multidimensional Fatigue Inventory 20, Hospital Anxiety and Depression Scale) (2;5;7-12) or disease-specific questionnaires (available for acromegaly (13-15), Cushing's disease (16-18) and growth hormone deficiency (GHD)(19)). Disease-specific questionnaires have been developed based on semi-structured interviews of individual patients using topics preselected by physicians. Afterwards the emerging topics were checked and modulated by the same physicians. Although patients' experience was included, the development has been controlled by the QoL perception of the physician from the beginning, instead of starting with QoL as formulated by patients.

In contrast, a valuable example of a research method which starts with the patient's perception, is focus groups research. Focus group research incorporates a small number of people (4-8 persons) discussing a particular subject in an informal group discussion. Unlike individual interviews, focus group interviews explicitly use group interaction as part of the method. This method is particularly useful in exploring people's knowledge and experience and can be used to examine not only *what* people think, but also *how* they think and *why* they think that way (20). Focus group methodology is frequently used to assess health and illness related topics, such as QoL, health care needs and experiences of everyday life in patients with chronic diseases (21-24). Furthermore, it has been used for the development of disease-specific QoL questionnaires (25;26) and to identify disease-specific QoL aspects (27-29).

Factors explaining persistently impaired QoL in patients with pituitary diseases are not well established, but are likely to be multi-factorial. Several studies revealed predictors (of aspects) of QoL, such as age, gender, tumor recurrence, non-replaced hypogonadism, non-replaced GHD, visual field deficits, sleepiness, joint complaints, clinical osteoarthritis, radiotherapy and delay of diagnostic process (8;30-35). Besides these biomedical predictors, we recently demonstrated that negative illness perceptions correlate with QoL in patients with acromegaly or Cushing's disease (10,47). We speculate that also other psychological or social factors can contribute to the persistently reduced QoL, i.e. unmet needs regarding care, which appear to be associated with QoL in other chronic diseases (36).

The primary aim of the present focus group study was to explore QoL as reported by patients treated for pituitary diseases. In addition, we aimed to identify potential factors that contribute to a decreased QoL. We hypothesized that focus group research would provide

ideas complementary to currently available diseases-specific QoL questionnaires, and would elucidate potential factors that contribute to QoL in pituitary diseases. This would give the opportunity to optimize biopsychosocial care for patients treated for pituitary adenomas, aiming to ultimately improve QoL.

METHODS

Subjects

Patients were recruited from the outpatient clinic of the department of Endocrinology and they were selected by their consultant endocrinologists. Patient selection was based on pre-specified criteria aiming at a focus group composition that would be representative for the chronic situation of the specific pituitary disease (and its sequelae) with respect to: 1) age, 2) gender (almost equal distribution of men and women, except for the CD group considering the high prevalence of CD in females), 3) time since diagnosis and 4) degree of medical complaints as estimated by the consultant endocrinologist, including a mix of cured and medically treated patients, if applicable, and a mix of patients dealing with hypopituitarism and those having normal pituitary function. Four groups were formed each consisting of 6 patients (Cushing's disease (CD), Non-functioning macroadenoma (NFA), acromegaly (ACRO), prolactinoma (PRL)), see Table 1. Group size and composition were chosen according to the published guidelines for focus group research (37).

The diagnosis and state of biochemical remission were confirmed in all patients, following previously described criteria (7;38-40). All patients gave written informed consent. The Medical Ethical Committee of the LUMC approved the research protocol.

Study design

The focus group meetings were chaired by a health psychologist (moderator), experienced in group discussions who took the role of an independent moderator (NGAK) (41-43). The investigator (CDA, psychologist) and a research intern (EK) observed both meetings, but did not participate in the discussions. All 4 groups met twice for a focus group discussion of ~2 hours each. The first meeting had the primary aim to get acquainted and to ensure a safe and confidential group setting in which everybody felt comfortable to speak and act freely. Patients were asked to introduce themselves, then the discussion continued with open-ended questions raised by the moderator about spontaneously reported issues. For example, when one participant spontaneously reported to be depressed sometimes, the moderator asked the other group members: "Are there moments when you feel depressed?" Based on the discussion of this first meeting, a topic list was formulated which was used during the second meeting (Appendix 1). During both meetings the moderator used open-ended questions.

Table 1. Demographic characteristics of pituitary patients (N = 24)

	Acromegaly (n=6)	**Cushing's disease** (n=6)	**Prolactinoma** (n=6)	**NFA** (n=6)
Age (years)	48.6 (36-65)	42.4 (25-58)	44.5 (34-54)	49.2 (27-64)
Gender (M/F)	3/3	2/4	3/3	3/3
Education:				
Low	0	1	0	0
Medium	2	1	2	2
High	4	4	3	4
Unknown	-	-	1	-
Duration of follow-up (yrs)	6.5 (2-19)	10.3 (1-23)	9.6 (2-20)	5.2 (1-12)
Disease severity at time of diagnosis:				
Tumor size (micro/macro)	2/4	6/0	2/4	2/4
Visual field defects	1	0	2	4
Treatment:				
Radiotherapy	0	1	1	1
TSS	5	6	1	3
Current suppressant medication	4	-	4	-
Hypopituitarism:				
Any axis	0	5	4	6
ACTH	0	3	2	3
GH	0	1	0	4
LH/FSH	0	1	0	2
TSH	0	3	1	4
ADH	0	0	0	1

Data are presented as median (IQR) or number.
Education classification: *low* elementary school, preparatory low-level applied education – *medium* preparatory middle-level applied education, higher general continued education, preparatory scientific education, middle-level applied education – *high* higher professional education, scientific education. TSS: Transsphenoidal surgery.
Current suppressant medication: Acromegaly (somatuline, somavert, sandostatine, octreolin), Prolactinoma (cabergoline, parlodel, norprolac).

Data analysis

Transcripts were analyzed following the steps of a grounded theory approach (44). First, two researchers (NDN endocrinologist, CDA psychologist) listened to the recorded discussions and carefully read and reread the transcripts. These two researchers independently performed open coding of the transcripts for each disease separately, using Atlas.ti 6.2 software. Discrepancies between coding were discussed and coding of transcripts of all groups as a whole was checked. As a result, categories were inductively identified from the data. In the second phase an axial coding method was performed, which is used to reflect on the properties of the categories (i.e. are categories applicable?) and to consider the relationships between the different categories (i.e. how are categories linked to each other?). The biopsychosocial model (45) was deductively used to reformulate categories. In the last phase data was integrated around the established categories and it was conceptualized how these categories may be integrated into a theory.

RESULTS (Figure 1, Table 2)

All patients were present during both focus group meetings, except one patient of the PRL-group who was absent during the second meeting, due to personal circumstances.

From the transcripts thirteen main categories of issues were identified. Nine categories corresponded to the biopsychosocial domains of QoL (46) (physical complaints, cognitive complaints, sexual problems, personality issues, psychological problems, negative feelings, social problems, work related problems and limitations in leisure activities). Four alternative categories were identified that might contribute to QoL (less effective coping strategies, negative illness perceptions, negative beliefs about medicines, unmet needs regarding care). Figure 1 presents the overlap and connections between the biological, psychological and

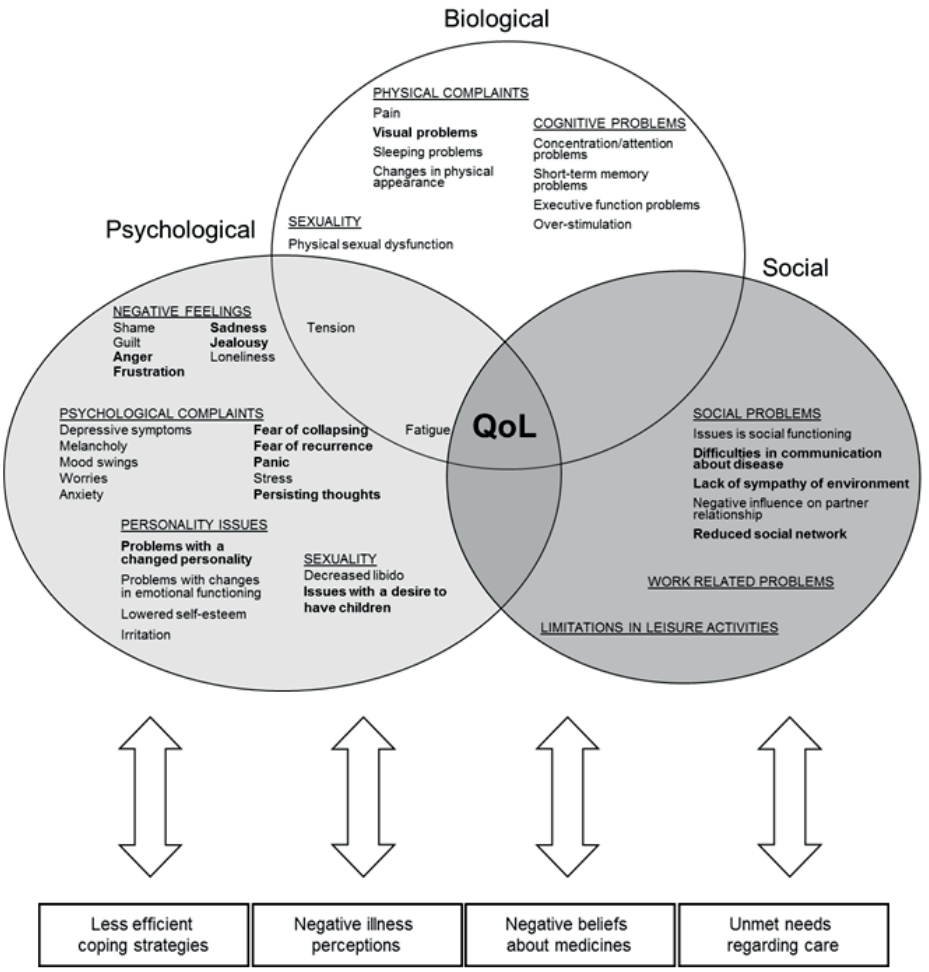

Figure 1.QoL in patients with pituitary diseases, as perceived by patients.
Italic: additional aspects which are not included in available disease-specific questionnaires.

social categories and the possible influence of the alternative categories. Table 2 summarizes the identified categories and the similarities and differences between the respective pituitary diseases, together with some representative quotes. Newly raised aspects are further elaborated below. Topics which are not included in available disease-specific QoL questionnaires (13-19) are highlighted in bold.

Physical complaints were fatigue, physical pain, sleeping problems, changes in physical appearance and **visual problems.** Fatigue was the most profound physical complaint in all groups. The cause of fatigue was not easily explained and it was attributed to their pituitary disease, their job or impaired sleep. The fatigue was both physical and mental. In addition, lowered muscle strength and impaired physical condition were reported. Sleeping problems were reported in all groups (except PRL). For example, difficulty with falling asleep due to persisting thoughts (CD)[Q1], or difficulty staying asleep due to sleeping in blocks of 2 to 3 hours (NFA). A long lag time after awakening was also reported (ACRO)[Q3]. Visual problems, such as tunnel vision, were reported (NFA), and the severity was related to fatigue. Some patients had problems sleeping in total darkness because of disorientation due to the visual impairment.

Cognitive problems were characterized by concentration and attention problems, short-term memory problems, executive functioning problems and a feeling of over-stimulation.

Sexual problems were physical sexual dysfunction, such as erectile dysfunction, decreased libido and **issues with a desire to have children.** Some patients reported inability to get an orgasm. Female patients reported menstruation problems (i.e. chronic menstruation), which interfered with sexual activity. (New) relationships were perceived to be affected by physical sexual dysfunction. Decreased libido (all groups) was discussed[Q12], although the cause was not unanimously attributed to the disease, but also to aging, a negative self-image, shame, physical pain and as a side effect of medication. The awareness of a decreased libido resulted in the fact that sexual intimacy was not initiated by the patient and therefore gave tension between partners[Q13]. A desire to have children and family planning were serious issues for some young women as they felt uncertain whether it would be possible to conceive at all, or alternatively whether they would be capable of caring for a child.

Psychological complaints were depressive symptoms, mood swings, melancholy, anxiety, stress, **fear of collapsing, fear of recurrence, panic** and **persisting thoughts.** Fear of collapsing was related to situations with higher temperatures and physical strain. Fear of recurrence was reported in all groups and it was provoked by physical complaints (flu-like symptoms or pangs in the head). Fear of recurrence was aggravated by discontinuation of medical treatment and by uncertainty about the cause of the adenoma. Patients reported

Table 2. Overview of QoL categories in different diseases and illustrative quotes

	CATEGORY	SUBCATEGORY	
			Illustration of complaint
Biological	Physical complaints	Fatigue*	Fatigue was the profound physical complaint. Lowered muscle strength and impaired physical condition were also reported. The nature of fatigue differed between the four pituitary diseases: either strange intense fatigue which took them by surprise and could disappear in just half an hour (PRL), severe fatigue requiring a two hour nap in the afternoon (CD) or extreme chronic tiredness with a "shaking" body (ACRO).
		Physical pain	Physical pain was especially reported by the ACRO-group, which included headaches, a tickling and inflamed sensation of the whole body, arthralgias with red thick joints. CD and NFA patients also reported joint complaints.
		Sleeping problems	Sleeping problems were reported, for example, difficulty with falling asleep due to persisting thoughts (CD)[Q1], or difficulty staying asleep due to sleeping in blocks of 2 to 3 hours (NFA). The perception of interrupted sleep was not always negative, since some patients liked easy waking in the morning[Q2]. A long lag time after awakening was also reported (ACRO)[Q3].
		Changes in Physical appearances	Changes in physical appearance were reported, with main feature weight gain. The ACRO-group experienced coarsening of appearance, with features as a bigger mouth, nose and cheeks, large spaces between teeth, big hands and feet being perceived as very negative[Q4].
		Tension*	Both physical and psychological tension were reported[Q19, Q20]
		Visual problems	
	Cognitive problems	Concentration/ attention problems	Concentration and attention problems and problems with mental focusing were reported by all groups. Concentrating was reported to be energy consuming.
		Short-term memory problems	Short-term memory problems were reported with word-finding problems and difficulty remembering names, while the long-term memory was generally intact.
		Executive function problems	Executive dysfunction was reported, such as decreased ability to formulate sentences, problems with multitasking, lowered processing speed and decreased ability to orientate[Q5]. Problems in keeping up with the speed of conversations were mentioned (ACRO)[Q6].
		Over-stimulation	A feeling of overstimulation was experienced and they mentioned difficulty to deal with large crowds.
	Sexuality	Physical sexual dysfunction	Physical sexual dysfunction such as erectile dysfunction was reported (PRL). Some male and female patients of the ACRO-group reported inability to get an orgasm. Patients reported menstruation problems (i.e. chronic menstruation), which interfered with sexual activity (NFA). (New) relationships were perceived to be affected by physical sexual dysfunction.

Bold: QoL which has not earlier been studied and which is not included in a disease-specific QoL questionnaire.
Grey: category which is earlier used in other disease-specific questionnaires for pituitary diseases.
* Category was mentioned biologically, as well as psychologically.

Reported by				Quotes	Nr
CD	ACRO	PRL	NFA		
x	x	x	x		
x	x		x		
x	x		x	*It takes time before I can get to sleep because I have to organize my thoughts first; thoughts about what is yet to happen and what I have to do.*	Q1
				On the one hand I think it is quite nice. I used to be able to sleep and wake up only when the alarm rang. Now I don't have the feeling that I'm lying down.	Q2
				If I am awakened in the morning because something has to happen, then my whole system becomes disrupted; I might as well forget the rest of the day.	Q3
x	x		x	*My appearance has changed, and it has not had a positive effect on me. I don't like the fact that my face has changed.*	Q4
	x			*When thinking about the things that I have to do, my whole body becomes tense.*	Q19
			x		
x	x	x	x		
x	x		x		
x	x		x	*When I was in an unfamiliar city, I walked through a shopping mall and I went in and out of shops, I couldn't really remember from which part I came or how I should walk back. After the operation, things go better, but it is still different to the situation before the operation.*	Q5
				When I am in a conversation, I want to keep up with the conversation, but I notice I just cannot.	Q6
x					
	x	x	x		

Table 2. Overview of QoL categories in different diseases and illustrative quotes (continued)

	CATEGORY	SUBCATEGORY	
			Illustration of complaint
Psychological	Psychological complaints	Depressive symptoms	Current depressive symptoms were discussed.
		Melancholy	Melancholy was reported, which was perceived to be caused by physical complaints.
		Mood swings	Mood swings were discussed[Q7].
		Worries	Some groups reported worries in relation to physical complaints and the possible progression of these complaints in the future[Q8].
		Stress	Patients perceived more stressful events than before the diagnosis, but also a higher sensitivity to stress, most pronounced in the CD- and ACRO-group.
		Fatigue*	Both physical and mental fatigue are reported.
		Anxiety	Patients reported (some) anxiety and panic attacks, associated with unexpected situations (CD)[Q9], or in relation to orientation problems (ACRO)[Q10].
		Fear of collapsing	
		Fear of recurrence	
		Panic	
		Persisting thoughts	
	Sexuality	Decreased libido	Decreased libido was discussed[Q12], although the cause was not unanimously attributed to the disease, but also to aging, a negative self-image, shame, physical pain and as a side effect of medication. The awareness of a decreased libido resulted in the fact that sexual intimacy was not initiated by the patient and therefore gave tension between partners[Q13].
		Issues with a desire to have children and family planning	
	Personality issues	Problems with changes in emotional functioning	Furthermore, changes in emotional functioning were reported, for instance being more sensitive to emotions (CD)[Q15], having extreme emotions (PRL)[Q16], or a flattened affect with less fantasy (e.g. daydreaming, fantasizing) (ACRO)[Q17].
		Irritation	In general patients reported to be less patient and to experience more irritability.
		Lowered self-esteem	A lowered self-esteem was reported, either initiated by the disease or already present before the diagnosis. The current experienced insecurity was mainly caused by functional limitations[Q18].
		Problems with a changed personality	

Reported by				Quotes	Nr
CD	ACRO	PRL	NFA		
x		x			
x	x	x			
x		x		*Within a short period of time your feelings fluctuate.*	Q7
	x	x		*I sometimes feel like an elderly-person, how will it be in ten years time? I worry about that.*	Q8
x	x	x	x		
x	x				
x	x				
x	x		*x*		
x	x	x	x		
x	x			*When friends invite me to go to the city, I already panic and I think "O no" then I have to do this and that the next day.*	Q9
				I panic terribly, when I am in the city or wherever I am. When I come out of a store I don't know whether I left the shop on my right or on my left. For instance when I am in a big shopping mall, I will stay at the same point when my friend goes to look at something.	Q10
x				*If I forgot to buy butter, then I have to immediately return to the stores to buy it, even though there's no need for it, because otherwise I would not be able to sleep a wink.*	Q11
x	x	x	x	*I don't have the need to have sex.*	Q12
				My libido is decreased; at a certain moment you come to a point that you doubt your relationship.	Q13
	x		x		
x	x	x		*I get very emotional very quickly. Someone saying "boo" to me is sufficient to make me cry. It can also be of happiness.*	Q15
				When I was angry, I became furious. When I had to laugh, I laughed hysterically. *In a way the emotional part is also beautiful.*	Q16
				Fantasizing about future plans or about nice things is decreased.	Q17
x	x		x		
x	x		x	*It is your awareness of your limitations that thwart you and makes you act insecure.*	Q18
x	x	x	x	*I am having difficulty with the fact that I have changed mentally and psychologically.*	Q14

Psychological	Negative feelings	Tension*	Both physical and psychological tension[Q19, Q20]
		Loneliness	Loneliness was reported in connection with fatigue or depressive symptoms.
		Guilt	Guilt was reported and this was especially felt in their partner relationship, since patients sometimes felt they were less able to pay attention to their partner or because of the decreased sexual libido.
		Shame	Patients reported shame because of physical sexual dysfunction, but also because of being ashamed of their body during sexual activity.
		Anger	
		Jealousy	
		Sadness	
		Frustration	

Bold: QoL which has not earlier been studied and which is not included in a disease-specific QoL questionnaire.
Grey: category which is earlier used in other disease-specific questionnaires for pituitary diseases.
* Category was mentioned biologically, as well as psychologically.

		x			*The whole day I am tensed.*	Q20
	x			x		
	x		x			
		x	x			
	x			x	*At first, I was really angry at my body. A failure in my body has let me down.*	Q21
		x			*I envy friends who look feminine and I envy friends when they get children.*	Q22
	x	x			*I have gone through a lot of sorrow in the last couple of years. All this because I discovered that I wasn't myself anymore and I couldn't do things that I could do.*	Q23
	x	x	x			

Table 2. Overview of QoL categories in different diseases and illustrative quotes (continued)

	CATEGORY	SUBCATEGORY	Illustration of complaint
Social	Work related problems		
	Limitations in leisure activities		
	Social problems	Issues in social functioning	Patients reported issues in social functioning. They felt insecure and nervous in social situations[Q24]. Moreover, they experienced some difficulties with social contacts[Q25].
		Negative influence on partner relationship	The whole process of diagnosis frequently had a negative influence on the partner relationship and some marriages had fallen apart during the time of diagnosis[Q28]. Also after treatment, relationships were negatively influenced by changed personalities and decreased sexual activity and libido. In addition, patients also reported negative influences on their family.
		Reduced social network	
		Difficulties in communication about disease	
		Lack of sympathy of environment	

Bold: QoL which has not earlier been studied and which is not included in a disease-specific QoL questionnaire. Grey: category which is earlier used in other disease-specific questionnaires for pituitary diseases. * Category was mentioned biologically, as well as psychologically.

Reported by				Quotes	Nr
CD	ACRO	PRL	NFA		
x	x	x	x		
x	x		x		
x	x			*I get tensed when I have to go to a birthday party. If I go then I have to socialise and do fun things – that is something that I find difficult. It is actually too much for me to cope.* *If I see 6 people waiting to pay near the cashier, I will not even enter the shop. I would rather go another time than wait impatiently in the line.*	Q24
				I have difficulty with social contacts. If the friendship does not work out, I don't bother anymore, it's an unpleasant vicious circle	Q25
	x	x	x	*He made the best of a bad bargain, Perhaps none of this would have happened if part of the care plan included teaching the partners of patients the effects the disease can have on someone's psychology. As a result, my partner could have had a better understanding with regards to this.*	Q28
x	x			*I had a large network of friends and relatives, but in the meantime I lost 98% of those people.*	Q29
				I have lost no one with whom I have discussed my disease as they have sympathy for my situation.	Q30
x	x	x	x	*Sometimes I walk a bit strange because of problems in my cartilage. Then I tell people that it will disappear sooner or later and that it was a result of doing too much sport.*	Q26
x	x		x	*My employer has all the brochures, but he puts them on a pile. He would prefer it if I quit the job and that I be replaced by someone who is healthier and who is able to earn money for him.*	Q27

Table 2. Overview of QoL categories in different diseases and illustrative quotes (continued)

	CATEGORY	SUBCATEGORY	
			Illustration of complaint
	Negative illness perceptions	Consequences	Patients reported a severe impact of the disease on their lives and told that they had underestimated the consequences[Q31]. They pointed out that factors such as age at diagnosis or duration of active disease prior to diagnosis may have influence the experienced impact. Some considered the influence of the disease on their life, personal development and life choices[Q32].
		Timeline	Perceptions of a chronic timeline were noticeable in the awareness of the irreversible damage to their body (ACRO)[Q33]. Furthermore, patients reported the experience of physical complaints, such as physical weakness (PRL), physical pain, and joint complaints arriving by fits and starts (ACRO) (cyclical timeline).
		Cause	Sometimes there was confusion about the cause of the pituitary adenoma, for example explanations were a fall, medication or congenital[Q34]. Furthermore, patients were wondering when the disease actually started[Q35].
		Cure/control	It was thought that stress played a major role in the origination of the adenoma and/or in the recurrence of the adenoma[Q36].
		Identity	Some patients wondered whether certain complaints, such as complaints of fatigue or influenza were caused by their pituitary disease, or that they experienced common complaints. Some refused to attribute certain complaints to their pituitary disease[Q37]. Others said that in a way, the complaints suited them[Q38].
	Negative beliefs about medicines	**Concerns**	
	Less efficient coping strategies	Withdraw	Some patients preferred to withdraw and to be alone sometimes[Q40].
		Overdoing	
		Problems with acceptance	
	Unmet needs regarding care	**Insufficient information**	
		Inadequate cooperation/ communication medical specialties	
		Absence of recognition	
		Dissatisfaction with other aspects of medical care	
Contributing factors			

Bold: category which has not been studied before in patients with pituitary diseases. Grey: category which has been examined earlier (by the studies of Tiemensma et al. (10;47)).

Reported by				Quotes	Nr
CD	ACRO	PRL	NFA		
	x	x	x	*It has had quite an impact, you have a house, a good job, and all of a sudden you are ill. Meanwhile you have lost your complete life. It controls your life completely, your whole day.*	Q31
				I was thinking, suppose if I didn't suffer from the disease – would my life have been different? Would it have been better or would I have made other choices? How has my personality developed as a result of my disease and medication?	Q32
	x	x		*The damage is long lasting. The symptoms in your joint, your mental limitations and other signs which are part of the disease remain with you lifelong.*	Q33
x			x	*I find it difficult to decide for myself what the cause is. Has the disease progressed slowly or was it always present?*	Q34
				Did I have it already during my puberty? Then I can understand why I was depressive then.	Q35
x				*I always have this feeling that stress plays a role in my life. I fear that something might grow.*	Q36
x	x	x	x	*I think it is a kind of excuse, I have to handle it myself. The diagnosis of 'Cushing's Disease' is insignificant.*	Q37
				All complaints have a cause, actually it suits me the way it is.	Q38
	x	x	x	*The lower the mess, the better*	Q39
	x			*I retreat every now and then to recover; I think it is a painful situation.*	Q40
x	x	x	x	*I try to do as much as possible; I prefer to rest for two days, instead of taking it easy.*	Q41
x	x			*I have not accepted it, I am still searching.*	Q42
x	x	x	x		
		x	x		
x	x	x	x	*I can discuss about my medication and basically everything with my doctor, but we don't really discuss about who I am from the inside.*	Q43
x	x	x		*The ideal training should teach one how you can keep stress under control.*	Q44
				What are the do's and don'ts to keep the disease under control?	Q45
				A psychologist can support those with acromegaly. He/she could prepare us in advance for what to expect	Q46
				My husband could not go through it alone. He really needed help.	Q47

panic attacks, associated with unexpected situations (CD)[Q9], or in relation to orientation problems (ACRO)[Q10]. Less established complaints were for instance that patients reported to be unable to let go persisting thoughts about pointless issues (CD)[Q11] and the perception of mental absence, foremost during the 'active' disease period (ACRO).

Personality issues were problems with changes in emotional functioning, lowered self-esteem, irritation and **problems with a changed personality**. Patients (all groups) reported a personality change to some degree[Q14], for example they experienced to be less approachable, more tolerant and more peaceful to other people, or more conscious of their feelings.

Negative feelings were tension, loneliness, guilt, shame, **anger, jealousy**, **sadness** and **frustration**. Patients reported to be more sensitive to anger (CD, NFA). Furthermore, they felt anger towards their own body[Q21]. Jealousy was noticed, i.e. due to the inability to do what healthy friends can do (ACRO)[Q22]. Sadness was associated with fatigue or emerged because someone was not feeling his usual self (CD)[Q23] and they reported to cry more easily. All groups (except NFA) felt frustration facing the persisting physical and cognitive complaints, especially when their medical doctors or the social environment turned a deaf ear to their complaints.

Social problems were issues in social functioning, negative influence on the partner relationship, **difficulties communication about their disease, a lack of sympathy of environment** and **a reduced social network.** All groups reported difficulty communicating about their disease, for instance because they did not want to frighten somebody or being looked at with pity. Patients used little tricks to avoid talking about their disease[Q26]. Frequently, patients only told the direct environment about their disease. Patients informed their present employer about their disease, but patients hesitated to tell a new employer, because they were afraid to be rejected for a new job. Unfortunately, patients in all groups (except PRL) often encountered a lack of sympathy, for instance by acquaintances, colleagues and employers[Q27]. However, this lack of sympathy was most of the time resulting from ignorance about the disease. Patients experienced that their social network declined (CD, ACRO)[Q29]. However, in some cases discussing the disease within their social network prevented the loss of friends[Q30].

Work related problems were experienced in all groups. Patients experienced changes in their work situation due to their disease. Some lost their jobs or were (partly) rejected as medically unfit. Reasons for these changes were diminished ability to function, to concentrate and to cooperate. Most patients currently work part-time.

Limitations in leisure activities were perceived in their ability to perform sports, due to their physical limitations (all except PRL). In addition, they experienced limitations in social activi-

ties, such as going to parties and on trips. They reported that these activities were energy consuming and that they had to take into account the extended resting time afterwards.

Negative illness perceptions were reported. Illness perceptions are defined as: "the beliefs that a patient holds about his/her health problems", influence how patients respond to their illness. They are conceptualized in the Common Sense Model of self-regulation (CSM) of Leventhal et al. (1980). Illness perceptions in patients with pituitary diseases are previously evaluated by Tiemensma et al. (10;47). In general, patients cluster beliefs about their illness around five cognitive components: *consequences, timeline, cause, control/cure and identity* (48). All components were spontaneously mentioned during the focus group discussions.

Negative beliefs about medicines were reported. Beliefs about medicines can be grouped into two major categories, beliefs about the *necessity* of prescribed medication and *concerns* about the potential aversive/side effects (49). In these discussions, **concerns about medications** were most dominant. Patients reported negative experiences with medication (e.g. negative effect on mood) and they reported beliefs about the use of medication changing their personality (PRL). Patients in the ACRO-group experienced the use of injections as awful. Some patients reported that they disliked the use of hydrocortisone, and therefore preferred to take a low dose[Q39].

Less effective coping strategies used by patients were withdraw, **overdoing activities** and **problems with acceptance**. Some patients felt it was difficult to let go feelings of frustration and reported the need for alcohol intake to relax (ACRO, NFA). All groups reported that they overdo their activities[Q41]. Some patients reported problems with acceptance of the disease and its consequences (ACRO, CD)[Q42].

Unmet needs regarding care were **insufficient information, better cooperation and communication between medical specialties, absence of recognition for certain complaints** and **dissatisfaction with other aspects of medical care**. The most prominent unmet need regarding care was insufficient information about the disease at diagnosis and during active disease (all groups). For instance, information about the adverse effects of medication (effect on personality), physical complaints, psychological complaints, cognitive complaints, sexuality and the ability to have children. They would have liked to be better prepared with regard to the impact of the disease and the overall short- and long-term consequences of being a patient with a pituitary disease. Furthermore, patients agreed that medical specialties should better cooperate and communicate together and that other medical specialists than endocrinologist should be better educated about pituitary adenomas (e.g. gynecologists, general practitioners).

All groups experienced absence of recognition for certain complaints by medical professionals, i.e. lack of response to complaints of sexuality, fatigue, and other physical complaints. Psychological, social and personal issues were hard to discuss[Q43].

To some degree patients were also dissatisfied with other aspects of medical care (CD, ACRO, PRL), since they reported a need for stress-management[Q44] and lifestyle recommendations[Q45]. In addition, there was a need for special care of physiotherapists, dietitans, medical sports experts and psychologists[Q46]. Support was not only needed for patients, but also for their partners according to patients[Q47].

DISCUSSION

In this focus group study in patients treated for pituitary diseases, we explored QoL as perceived and discussed in representative patient groups. This study puts forward new QoL aspects from the patient's perspective, which are not included in the currently available disease-specific questionnaires, and identified factors which may contribute to decreased QoL. The primary aim was to explore disease-specific QoL as reported by patients treated for pituitary diseases. Earlier qualitative studies used semi-structured interviews about preselected topics to develop disease-specific QoL questionnaires (i.e. CushingQoL, Tuebingen CD-25, AcroQoL, QoL-AGHDA) (13-19). These topics can be categorized according to the biopsychosocial approach of QoL: (1) *physical problems,* (2) *psychological problems*, (3) *social problems*. Although the majority of these dimensions also emerged during the focus group discussions, new QoL aspects were also identified.

Newly raised physical issues were the presence of visual limitations, which is indeed a common symptom in patients treated for pituitary adenomas (1), but which is not included in available disease-specific QoL questionnaires. Uncovered psychological problems were issues with a desire to have children and family planning. At present, this issue is not incorporated in existing disease-specific QoL questionnaires, although many patients are of reproductive age. Furthermore, patients reported that they were unable to let go persisting thoughts, and had feelings of panic and fear. The reported fear of recurrence of the adenoma, is also frequently seen in cancer survivors (50) and is usually associated with increased use of health care services (e.g. a greater number of outpatient visits and emergency room visits) (51). Interestingly, this fear may be neglected by the physician, since they consider adenomas to be benign. Other uncovered psychological problems were the feeling that their personality was changed and feelings of anger, jealousy, sadness and frustration. Additionally revealed social problems were issues with communicating about the disease, facing a lack of empathy of others and a reduced social network. These physical, psychological and social issues were not included in earlier disease-specific QoL questionnaires. In conclusion, disease-specific QoL as formulated in available disease-specific QoL questionnaires for pituitary diseases could be further elaborated by incorporating the patient's perspective.

The second aim of our study was to identify factors that may contribute to a decreased QoL. Recent papers discussed the presence of negative illness perceptions and ineffective coping strategies (10;47;52). The present study revealed examples of negative illness perceptions and less effective coping strategies, but also negative beliefs about medicines and unmet needs regarding care. We believe that further exploration of the significance of these uncovered factors is relevant for the care of patients with pituitary adenomas, since these factors may affect QoL (10;36;47).

Concerns about medication and unmet needs regarding care were not previously described in patients treated for pituitary adenomas. In a study by Horne and Weinman it was found that concerns about adverse effects of medication were significantly associated with non-adherence to medication in patients with asthma (53). Considering the large part of patients with pituitary diseases that is treated with substitution therapy and medication, our findings suggest that physicians should be aware of, and adequately cope with these concerns. Furthermore, medical experts and other healthcare providers could play a role in meeting patient needs by being aware of the reported unmet needs. This awareness could improve the communication and care for patients treated for pituitary diseases. In addition, the patient's perspective of QoL explored in this study can be helpful for medical experts in their communication with patients, since it describes experiences, rather than numbers provided by QoL questionnaires. Patients reported an explicit need regarding care, such as stress-management, psychological care, and physiotherapy and nutrition and sports recommendations. Experts in these fields could play a major role in meeting this need, for instance by offering self-management interventions (SMI) including these aspects. It is found that SMI's positively affect well-being of patients suffering from chronic conditions (e.g. asthma, diabetes, arthritis, Parkinson's disease) (43;54;55). Obviously, objectives of SMI's differ between various diseases. For instance, SMI's for asthma aim to monitor symptoms and to improve adherence to medication, and SMI's for diabetes tend to focus on lifestyle issues. These differences in focus result in a range of different contents and methodologies in SMI's (56). The information provided in this study could be used for the adjustment of a SMI for patients treated for pituitary diseases.

There are some limitations to this study, all largely due to general limitations of focus group methodology. For instance, a dominant participant with his/her own agenda could have influenced the groups discussions. Nevertheless, the moderator aimed to prevent this by giving each patient equal space to speak. Although we aimed at a representative group composition able to reflect a broad range of experiences, a selection bias is inevitable. Moreover, with four different focus groups we considered the number of included patients adequate for conclusions for pituitary diseases in general. There was a considerable overlap in reported issues between the groups, but we also identified differences between the various pituitary adenomas. However, since there was only a single group per specific disease, we were unable to draw firm conclusions about Cushing's disease, Non-functioning pituitary

macroadenoma, acromegaly, and prolactinoma specific issues. Future quantitative research in a larger group of patients is needed to further evaluate the differences between groups and to determine the importance of each aspect to QoL. This could also give more insight in the potential influence of clinical characteristics, such as the influence of pituitary deficiency, disease severity and duration of follow-up.

In conclusion, this focus group study showed disease-specific QoL as formulated and perceived by patients treated for pituitary diseases. Furthermore, it uncovered potential contributing factors. The information provided in this study can be used for developing additional items for disease-specific QoL questionnaires and for the development of a SMI aiming to improve QoL in patients treated for pituitary diseases.

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TOPIC LIST APPENDIX 1

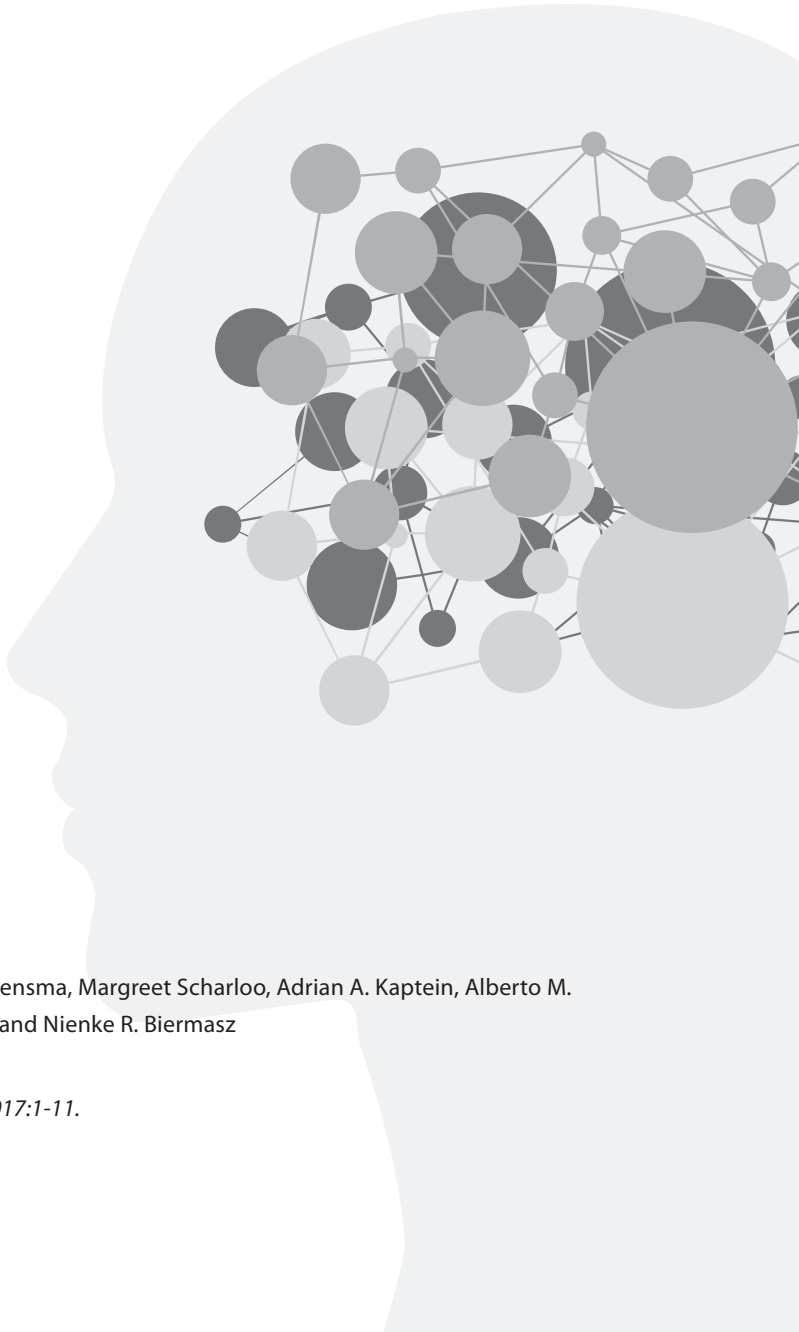
- Physical functioning
- Mood
- Emotions
- Stress
- Relationship
- Sexuality
- Social functioning
- Employment

Final questions (specifying unmet needs):

1. Given all of this, what would you prefer to have known / to have had after receiving the diagnosis?
2. What is your advice for someone who just received the diagnosis?

CHAPTER 12

The partner perspective of the impact of pituitary disease: looking beyond the patient



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ABSTRACT

People with pituitary disease report impairments in quality of life. The aim of this study was to elucidate the impact of the pituitary condition on the lives of partners. Four focus groups of partners of people with pituitary disease (Cushing's disease, non-functioning adenoma, acromegaly, prolactinoma) were conducted. Partners mentioned worries related to the pituitary disease and negative beliefs about medication, coping challenges, relationship issues, social issues, and unmet needs regarding care. This study emphasizes the importance of not only paying attention to psychosocial well-being of people with pituitary disease, but also to their partners.

INTRODUCTION

Pituitary adenomas can be considered a rare disease with an estimated prevalence of 78 to 94 cases per 100,000 individuals, and an incidence of four cases per 100,000 individuals (1). These benign tumours on the pituitary gland can result in classical medical conditions, such as Cushing's disease (CD), acromegaly (ACRO), prolactinoma (PRL) or clinically non-functioning pituitary adenoma (NFA). These conditions can be categorized by etiology. For instance, CD is referred to an overproduction of cortisol and is related to hypertension, changes in physical appearance and proximal muscle weakness. ACRO is characterized by an overproduction of growth hormone, and is related to physical disfigurement, mainly involving the face, hands and feet. PRL is featured by an overproduction of prolactin resulting in milk production by the breast and reduced libido in both men and women, and menstrual problems in women. Although people with NFA are not exposed to hormone excess, they may suffer from the mass effects of the adenoma resulting in symptoms such as visual field defects and headaches. Pituitary adenomas can be treated by surgery, and sometimes additional medical treatment or radiotherapy when needed. As a consequence of the mass effect of the adenoma and/or the treatment, the pituitary can be damaged resulting in hormone insufficiency. When this is the case, people receive life-long replacement therapy (2). People with a pituitary adenoma report impairments in physical functioning, as well as in psychosocial functioning, which usually improve after biomedical treatment, but which do not appear to normalize (3). During the chronic state of their disease people still report impairments in quality of life (QoL) (4-7). Considering these persistent impairments and the life-long medical (replacement) therapy, pituitary disease can be considered a chronic condition. In a recent qualitative focus group study these QoL impairments have been further elucidated in people with CD, ACRO, NFA, and PRL (8). They reported psychological complaints, problems with personality changes, issues regarding sexuality, and a negative impact on the relationship with their partner.

Weitzner and Knutzen (1998) reviewed literature on caregiving in dementia and cancer, and although the characteristics of these diseases are considerably different compared to pituitary disease, they suggested that there might be some issues that are also applicable to caregiving and family issues in pituitary disease. For instance, the authors reported that a major primary stressor in caregiving for people with dementia is the patients' disruptive behavioural problems (e.g. personality changes, agitation), and suggested that this stressor has general applicability to caregiving for people with pituitary disease. Furthermore, the authors describe that when caregiving continues over a longer time period, changes in social support become more persistent and are less likely to return to the premorbid situation (9). To the best of our knowledge, there is one qualitative study in partners of people with pituitary disease, which partially confirmed the postulations of Weitzner and Knutzen. This qualitative study by Dunning and Alford (2009) explored experiences of partners of people with pituitary disease using a focus group and interviews (n=12 partners). It was reported that the partner sometimes became annoyed by the tiredness and mood swings of the ill

partner, because there was no obvious cause. Some partners felt they had to take on extra responsibilities at home and managing the children. They were aware of the burden on their family, but they felt unable to cope emotionally or physically. However, in some cases the quality of the relationship was enhanced (10).

From quantitative QoL studies in partners of people with other chronic diseases it is known that partner QoL is negatively affected (11-14). From previous research it is also known that the role of the partner also strongly influences QoL of people with chronic disease. For instance, unsupportive behaviour of partners was associated with more distress in women with early stage breast cancer (15). On the other hand, solicitous behaviour of partners of people with chronic fatigue syndrome negatively affected improvement in fatigue and disability during cognitive behavioural therapy (16).

People with a chronic disease, as well as their partners, develop representations of the disease i.e. illness perceptions. These illness perceptions can be categorized around five common themes: identity, cause, timeline, consequences, and cure/control (17). Illness perceptions have been shown to exert a substantial influence on coping and QoL (18). In addition, addressing maladaptive illness perceptions has been shown to result in improvements in outcome measures (19;20). It is possible that illness perceptions of persons with a chronic disease differ from the ideas of their partners. For instance, partners of people with primary adrenal insufficiency, i.e. Addison's disease (AD), were more pessimistic about the timeline of the disease than the ill persons themselves. Partners were also more negative about the curability/controllability and the consequences of the disease. Moreover, dissimilarity in illness perceptions between persons with AD and their partners was associated with adaptive outcomes of the ill person (21). Illness perceptions were also different between people with Huntington's disease and their partners, with partners' beliefs about a longer duration of the disease and less belief in cure being associated with higher vitality rating of the ill persons (22), suggesting that partners who are realistic (even if negative) about the possibilities for cure and the long-lasting timeline of the disease might be beneficial.

In view of the persistent QoL impairments in people with pituitary disease (e.g. psychological complaints, personality changes, issues regarding sexuality), and the small number of studies in partners of people with pituitary disease, the aim of the present study was to explore the impact of the pituitary condition on the lives of partners. In the present study we used focus group interviews, which incorporate group interaction as part of the method. Focus groups are particularly useful in exploring people's experiences and knowledge, since it does not only assess what people think, but also the reasons why they think that way, and how they think (23). Focus groups are commonly used in illness related topics, such as QoL and healthcare needs in people with chronic disease (24;25), and disease and treatment experiences in caregivers of ill people (26;27). We hypothesized that in accordance with previous literature, partners of people with pituitary disease would also report a negative impact of the medical condition on their lives, including issues that are similar to partners of

people with chronic disease in general, but potentially also disease-specific issues that are more relevant for partners of people with pituitary disease.

METHODS

Participants

Partners who were willing to discuss the influence of the pituitary condition on their lives were recruited via their ill partners from the outpatient clinic of the department of Endocrinology, Leiden University Medical Center, the Netherlands. Seven (35%) of the participants were partners of people with pituitary disease included in a previous focus group study (8). Participant selection was aimed to result in a sample that would be representative of the partner population (e.g. regarding age, gender, education, and duration since diagnosis). Four focus groups were formed per disease (CD, ACRO, NFA, PRL). Recommendations for focus group sizes vary considerable, but it has been stated that groups with three to eight participants work best for generating rich discussions (28). Therefore the present focus groups consisted of four to six partners (i.e. CD:P1-P5, ACRO: P1-P5, NFA:P1-P6, PRL:P1-P4).

All participants gave written informed consent. The Medical Ethical Committee of the LUMC approved the research protocol.

Study design

The focus group conversations were chaired by a health psychologist (moderator), experienced in group discussion (NGAK). The investigator (CDA, psychologist/researcher) observed the focus group meetings, but did not participate in the discussions. Each of the four groups met twice for a discussion of ±2 hours. The focus group conversations took place in September 2012 and were held in a meeting room at the LUMC. The first meeting had the primary aim to get acquainted and to ensure a safe and confidential setting. Participants introduced themselves and then the discussion continued with open-ended questions suggested by the moderator. Based on the issues raised during the first meeting, a topic list was formulated for the second meeting (Supplement 1).

Data analysis

Data was analysed using an experiential thematic analysis following the six steps proposed by Braun and Clarke (2013). First, the audio-typed focus group conversations were typed out verbatim. Second, the transcripts were read and reread by the first and second author (JT psychologist/senior researcher, CDA psychologist/researcher) in order to get familiar with the data, and potential items of interest were noted. Third, initial codes were produced from the data and the entire dataset was coded. Discrepancies between coding were discussed, and resolved by consensus (i.e. JT, CDA). Atlas.ti 6.2 software was used for managing and ana-

lysing the data. Fourth, codes were sorted into potential themes. Fifth, preliminary themes were reviewed and a thematic map was created considering the formation of themes and subthemes. Extensive revision of themes was performed by splitting, merging and renaming themes. Finally, (sub)themes were further defined and named.

RESULTS

Twenty partners participated in the focus group discussions (11 females) and were present during both focus group meetings. Age ranged from 29 to 69 years (mean 48 years). Duration of follow-up ranged from a few months to 27 years (mean 9 years). After a total of eight focus groups (4 groups x 2 meeting) in our view, no new issues were discussed and data saturation was reached. From the focus group conversations, five themes were derived: worries related to the pituitary disease and negative beliefs about medication, coping challenges, relationship issues, social issues, and unmet needs regarding care (Figure 1). The current study envisioned to evaluate the present impact of pituitary disease. Interestingly, during the focus group conversations partners frequently referred to the stressful and intense moments experienced during the period of diagnosis, suggesting that this event still is an important issue. However, retrospectively evaluating this period of diagnosis did not match the scope of the research and data about this topic were therefore not incorporated.

Table 1. Demographic variables of participants

	Patients' pituitary disease:				
	Total (n=20)	**CD (n=5)**	**ACRO (n=5)**	**NFA (n=6)**	**PRL (n=4)**
Gender (M/F)	9/11	3/2	3/2	2/4	1/3
Age (years)	48 (39-57)	52 (36-56)	46 (43-66)	50 (38-61)	40 (35-48)
Duration of follow-up (years)	8 (3-13)	8 (7-18)	4 (3-22)	5 (2-9)	12 (3-18)
Education					
Low	2	0	1	1	0
Medium	6	1	3	0	2
High	12	4	1	5	2
Marital status					
Living together	3	1	0	1	1
Married	17	4	5	5	3

Data are presented as median (IQR) or number. CD=Cushing's disease, ACRO=Acromegaly, NFA=Non-Functioning pituitary adenoma, PRL= Prolactinoma.

Worries related to the pituitary disease and treatment

Worries related to the pituitary disease: Partners reported concerns about the current health status of the ill partner. For example, worries about something happening to the ill partner (e.g. too low cortisol levels resulting in a life threatening situation, which is named an Ad-

disonian crisis) when the partner is not around, but also concerns about how the ill partner is feeling that day. Partners also brought up concerns about the future, such as whether new problems will arise or whether existing problems will worsen. Another aspect was fear of recurrence. For example, when new symptoms are being experienced, partners wonder whether the new symptoms indicate tumor growth, recurrence of the tumor, or possibly something else. Partners also mentioned concerns about the possible heritability of the disease *"The fear that you pass it on to your children is very scary. We have done some research but there is almost no chance, at least in our case. But my son had lots of headaches last year, then I'm like okay, well, now what?"* (PRL-P2).

Negative beliefs about medication: Partners reported worries related to medication e.g. about the effectiveness of suppressive medication in the future and uncertainty about possible side-effects: *"I am anxious about the medicine use in the future, what if the medication doesn't work anymore at a certain moment, then you have to search for another treatment"* (ACRO-P4). They reported a strong negative attitude towards the medication, with the most negative thoughts mentioned in the PRL group. The partners commented on the negative effect of medication on the character of the ill partner (e.g. flattened affect, no highs and lows anymore): "*The moment he stops his medication I see my old husband. But that disappears as soon as he starts again"* (PRL-P2) and "*I think to myself: there goes another heap of poison*" (PRL-P1). Medication use was perceived as having a negative effect on sexuality *"There is certainly a big difference in sexuality between before and after the medication for the illness. That was quite difficult, but I knew there was that connection and that medication was the cause. I did not suffer from relationship problems or uncertainty, because I had that knowledge"* (PRL-P4).

Coping challenges

Uncertainty about accommodating or encouraging the ill partner: Many partners indicated difficulty in deciding when to accommodate the complaints experienced by their partner (e.g. fatigue) and when to encourage their partner to manage certain complaints by encouraging engagement in specific activities. Partners indicated that this difficulty improved over the years. "*It is difficult to determine when you need to be that shoulder to cry on, when you need to pull somebody up, or when to say 'don't be silly, get up, and do it'*" (CD-P5).

Making adaptations: Many partners reported adapting their own behaviour to accommodate the complaints of their ill partners. For example, taking on specific tasks and providing extra protection for their partner. "*I try to protect her every now and then*" (NFA-P2) and (another partner) "*We now have a young family, so that is very busy, it's half a pace faster than he can handle*" (CD-P2). Partners tried to protect the ill partner by not talking about difficulties experienced at work, since this potentially could be distressing for the non-working ill partner. Limiting potential topics of discussion led to feelings of inequality in the relationship. Furthermore, partners adjusted certain activities to the situation at hand "*My partner no longer drives, I always have to. Sometimes I feel like a taxi driver*" (ACRO-P1) and "*I cannot*

take her for a walk on the beach, because that won't work. But I can take her for a walk in the city with a pair of crutches" (ACRO-P4). Partners often felt that making such adjustments provided necessary support for the ill partner. They felt their ill partner was the weaker one. This is why partners were inclined to protect their ill partner: "*You are the one taking the blows*" (ACRO-P1). Partners reported feeling inhibited by the consequences of the disease, and feeling pressured to make certain decisions in specific situations. Interestingly, many partners were putting it all in perspective "*If my partner would be manic depressive, I would not recognize her. With her current medical condition, however, I can still recognize my wife, so it is still the same woman. This is incredibly helpful for me, because I can see whom I fell in love with*" (ACRO-P1).

High sense of responsibility: Partners reported they felt more responsibility in multiple contexts, which may result in adaptation of their own behaviour (see previous section). For example, partners felt responsible when it came to being well-informed "*because if something happens, you are the one who needs to act*" (NFA-P5). In addition, a (partial) loss of income of the ill partner may have resulted in a larger financial responsibility for the healthy partner. Furthermore, partners had difficulty determining their own limits. Many felt that they should show understanding and empathy, but also that they should maintain their own well-being (i.e. being clear about their limits).

Differences in coping styles: Partners found it difficult when their own coping techniques did not match those of the ill partner. For example, the ill partner would rather not talk about the disease and deny certain consequences, while the partner may feel the need to talk about it (see also next section).

Relationship issues

Changes in the relationship: Relationship difficulties sometimes arose during active disease and treatment periods. Partners reported feelings of inequality and the emergence of perceptions of a counselor-patient relationship. The skewed relationship usually returned to a balanced one over time. Some partners mentioned that their relationship became stronger because they fought together to get through the disease process: *"Our relationship has become very strong, because we fought the disease together and we came through together"* (CD-P5). Other partners reported a lasting negative impact on their relationship, for instance inequality on some fronts (i.e. there is still somewhat a counselor-patient relationship), or a general change in the relationship "*I find that it changes your relationships anyway, yeah, the positivity is gone*" (PRL-P4).

Communication with partner: Partners reported needing to express sensitivity in communicating when the ill partner was suffering from mood swings. Uncertainty about the ill partner's response during mood swings often led to tensions. Partners reported being able to talk about most topics, although issues related to sexuality were harder to discuss.

Viewing the partner differently: Some partners reported viewing their partner differently. For example, partners found their ill partner less attractive due to the changes in their rela-

tionship (i.e. shifting towards a counselor-patient relationship). However, partners also found their ill partner more beautiful, because they were proud of the way their ill partner coped with the consequences of the disease. Partners reported having great difficulty with the character changes of the ill partner (PRL) "*She/he is still my best friend, but she/he changed from a very positive person to somebody who is very black-and-white*" (PRL-P2), while other partners reported a positive character change: *"I tell my partner that he/she has changed considerably, became sweeter, and even more attractive to me"* (NFA-P3).

Issues regarding sexuality: Some partners reported that sex/intimacy with their ill partner improved compared to the past, and that it became more valuable. Other partners reported that sex/intimacy decreased during active disease, and that it recuperated but did not normalize "*Our sex life took quite a hit*" (NFA-P3).

Issues with the desire to have children: Partners reported concerns about the inability to conceive, either currently or in the past "*You have a certain expectation about your life, and you need to adjust that expectation*" (PRL-P2).

Social issues

Difficulties in communicating about the disease: Difficulties in talking about the disease, as well as talking about potential consequences were reported. Partners had a hard time determining whom to tell about the disease. When partners decided to tell somebody about the disease, they found it difficult to explain what was going on "*It is like you lost your arm, which will never grow back. Other people then understand it cannot be reversed, because that is often the question*" (ACRO-P1). Some partners reported giving shorter answers over time when questions about the disease came up because they faced misunderstanding from people around them.

Lack of sympathy from the social network: Partners reported that people in their social network asked questions about the disease with the assumption that it would get better. Similarly, they felt that symptoms were downplayed by their social network "*When a friend says: sure, I experience the same symptoms every now and then, I think I am suffering from the same disease*" (NFA-P2) or "*People in your social environment say: it's not malignant, so it is nothing*" (PRL-P4). The social network does not understand why people with pituitary disease and their partners cannot participate in certain activities. Some partners reported loneliness due to the misunderstanding in their social network. Partners mentioned that the ill partner does not look sick, which could be the source of the misunderstanding in their social environment. Some partners also indicated that they are tired of being asked about the well-being of their ill partner, and that they themselves are rarely asked about their own well-being.

Changes in social network: Partners reported that their social network had shrunk or at least had changed in a negative way.

Negative impact on family: Partners were concerned about the impact on their family. For example, expression of increased irritability around their children "*We currently experience*

that she/he is very tired and her/his patience runs out quickly. This is also towards the children" (NFA-P4). Partners also mentioned that their children were concerned about the ill partner.

Negative impact on work: Partners reported they sometimes take time off work to accompany the ill partner to the doctor. Some partners even quit their job to keep everything afloat at home and to create stability (a somewhat forced choice).

Unmet needs regarding care

Insufficient information: Partners felt inadequately informed about the disease and its treatment, and felt they did not get clear answers to some questions. Partners would have liked to be more involved in the information process *"If it is explained to me how it works psychologically, than I would have a lot less difficulty, less burden, and it would cost less energy. That would benefit the relationship when it comes to what you have to offer a partner"* (PRL-P4). Furthermore, partners mentioned that doctors should use less jargon when providing information to facilitate understanding.

No recognition for certain complaints: Partners experienced insufficient recognition for certain complaints, such as questions pertaining to the psychosocial aspects of the disease, questions about practical issues such as contraceptives, and questions about medication use abroad. Partners also felt that certain aspects of the treatment were easily dismissed, for example life-long medication use "*Your pituitary is damaged and it is possible that partial removal of the pituitary is necessary. However, this was easily dismissed with statements about 'eliminating the effects of partial pituitary removal with medication', and 'everything will be alright'*" (NFA-P3).

Dissatisfaction about aspects of medical care: Partners would like additional guidance with psychosocial issues (e.g. medical psychologist, social worker, coach) or for example a help line to talk and get things off their chest. Partners in the PRL group mentioned they would like to learn the best way to deal with potential psychological symptoms of their ill partners. Partners would have liked more guidance during active disease and treatment. For example, guidance for children of parents with a pituitary adenoma, but also advice on how they can best guide their children. There was also a need for peer support. Partners would like to receive help and guidance in how to best support the ill partner. Other partners indicated they do not want to be a 'life coach' for the ill partner, since this could disrupt the balance in their relationship.

DISCUSSION

This explorative focus group study in partners of people with pituitary disease provided an overview of the impact of the pituitary disease on their lives. The main issues reported by partners were that they were worried about the pituitary disease, had negative beliefs about the medication, and that they encountered challenges in coping with the consequences. Fur-

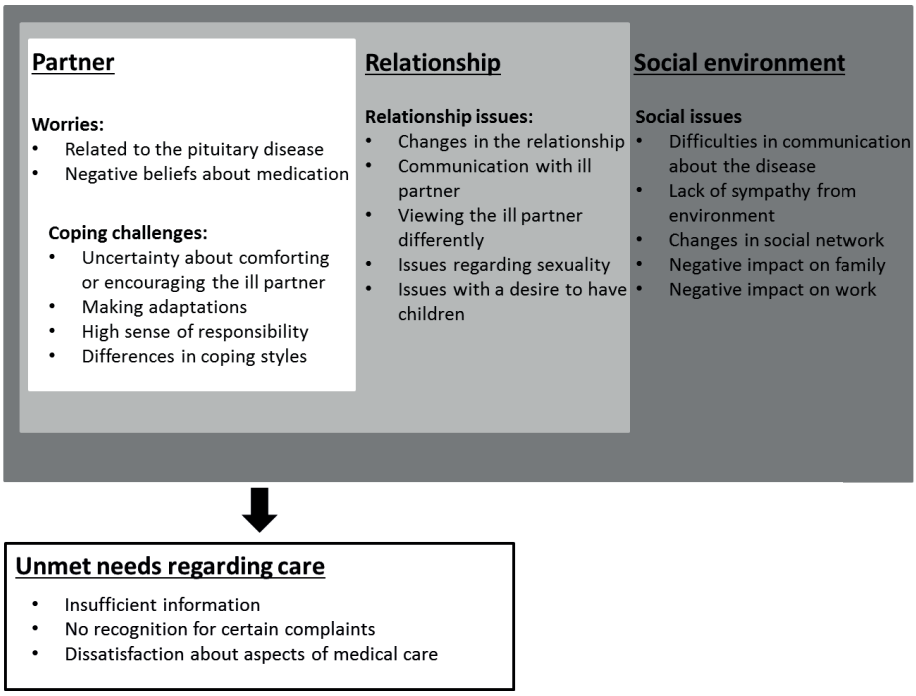

Figure 1. The partner perspective of the impact of pituitary disease.

thermore, partners experienced issues in their relationship and in their social environment. Considering aspects of medical care, they felt inadequately informed about the disease and its treatment, they experienced insufficient recognition for certain complaints, and they would like to have additional guidance (e.g. psychological support).

Weitzner and Knutzen (1998) speculated about issues for caregivers of people with pituitary disease based on observations in caregivers for people with dementia or cancer (i.e. stress due to disruptive behavioural problems e.g. personality changes, and changes in social support). Both aspects were reported by partners in the present study; however some partners considered the personality changes of their ill partner bothersome, while others perceived these changes rather positive. Similar to the results of the qualitative study of Dunning and Alford (2009) in partners of people with pituitary disease (10), the partners in the present study reported the negative effects of the mood swings and fatigue of their ill partners. They also reported the higher sense of responsibility and negative impact on their family life. On the other hand, enhanced relationships were also reported. Furthermore, the partners in the study of Dunning and Alford felt excluded from much of the decision-making process and reported that they had to rely on the information given by their ill partner. This issue somewhat resemble what the partners in the present study reported i.e. they would have liked to be more involved in the information process. Furthermore, in a qualitative

study in people needing testosterone replacement and their partners it was observed that partners reported changes in their relationship i.e. they reported loneliness, less affection, and they felt unwanted sexually (29). These observations are in accordance with our finding that partners reported that sex/intimacy decreased during active disease.

Partners reported unmet needs regarding care including insufficient information, no recognition for certain complaints, and dissatisfaction about aspects of medical care. Health care professionals could play a role in fulfilling these unmet needs by first and foremost being aware of these unmet needs. This awareness could facilitate the communication with patients and partners, and encouraging the provision of patient (and partner)-centered care. Furthermore, partners explicitly reported a need for additional guidance regarding psychosocial issues, such as support from a health psychologist, social worker, or coach. Therefore, experts working in this field should be incorporated in the multidisciplinary team of healthcare professionals taking care of patients with pituitary disease. In addition, a self-management programme for patients and their partners could support them to cope with the disease and its consequences together.

It should be noted that some of the issues reported by partners of people with pituitary disease are also observed in partners of people with other chronic diseases. For instance, in a recent focus group study in partners of people with prostate cancer, partners reported a need to be involved in the treatment process, reported issues in how to support one's husband (who is experiencing a loss of masculinity), problems regarding incongruent coping responses between partners, and constrained communication between partners (30). Furthermore, mainly of the enlisted issues for partners of people with chronic disease in general in the review of Rees *et al.* (2001) were also reported by the partners of the present study e.g. fear of the future, deterioration in the partner relationship and sex life, concern about suffering of the ill partner, and social disruption (31).

Although the majority of the reported aspects may also be observed in partners of people with chronic disease in general, it is tempting to speculate that some of these issues are more pronounced in partners of people with pituitary disease. For instance: the negative beliefs about medication, since the majority of the patients need life-long (daily) replacement therapy and/or suppressant medication. Issues regarding sexuality and the desire to have children can also be more pronounced considering the important role of the endocrine system in fertility and sexuality. Finally, we postulate that the reported lack of sympathy of the environment is more pronounced in partners of people with pituitary disease than in other chronic diseases, considering the fact that a pituitary adenoma is a rare disease and relatively unknown in society.

The limitation of research reflexivity could potentially be found in the previous research by our research group into the psychosocial impact of pituitary disease (3;8;32-35). Although we strongly attempted to approach the partners' stories unprejudiced, it might be that our preconceived views of psychosocial issues in patients with pituitary disease have influenced

the research process. Furthermore, we aimed to have a representative group composition able to reflect a broad range of experiences, however selection bias may be inevitable. Future quantitative research is needed to examine well-being of partners of people with pituitary disease. This would provide the opportunity to examine how well-being of partners of people with pituitary disease relates to well-being of partners of people with other chronic diseases (11;13;14), as well as whether illness perceptions of people with pituitary disease are similar to the perceptions of their partners.

In summary, this explorative focus group study in partners of people with pituitary disease illustrates the negative impact of pituitary diseases on the lives of partners. This study emphasizes the importance of not only paying attention to the psychosocial impact of people with pituitary disease during medical consultation, but also to their partners. Furthermore, information obtained in this study can be used for the development of a disease-specific questionnaire for partners of people with pituitary disease, in order to quantitatively assess their well-being, as well as for optimizing psychosocial care not only for people with pituitary disease, but also for their partners.

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SUPPLEMENT 1. TOPIC LIST

Focus group 1

Introduction by saying:
- Welcome
- Aim of the focus group conversation is to explore experiences of living with a person with a pituitary disease and the impact on their lives
- All conversations are confidential
- Conversations will be audiotaped and typed-out verbatim
- Please avoid talking over each other
- Avoid non-verbal communication (i.e., nodding), since this cannot be audiotaped
- Ask everyone to introduce themselves and say briefly something about work, family composition, hobbies, when was your partner diagnosed with the pituitary condition

Starting question:
- What do you encounter in daily life related to the pituitary condition of your partner?

The discussion will be continued by using open-questions sometimes followed by closed questions that act as prompts for discussion

Finishing conversation:
- Ask whether participants want to add a final remark to the conversation.
- Saying that the next focus group meeting will be within 2 weeks at a certain time/date.

Focus group 2

Introduction by saying:
- Welcome
- Aim of the present focus group meeting is to have a more in-depth conversation based on issues raised during the previous meeting
- All conversations are confidential
- Conversations will be audiotaped and typed-out verbatim
- Please avoid talking over each other
- Avoid non-verbal communication (i.e., nodding), since this cannot be audiotaped

The discussion during the second focus group meeting was held by using a topic list (below) based on the first focus group meeting. The discussion was continued by using open-questions sometimes followed by closed questions that act as prompts for discussion.

Topic list

Mood

How does the pituitary condition of your partner affect your mood?
- Anxiety?
- Depressive symptoms?

Emotions
- Anger?
- Guilt?
- Frustration?
- Tension?
- Loneliness?
- Insecurity?
- Sadness?

How do you cope with emotions/tension?

Stress

How do you experience stress?
How do you cope with stress?

Coping
Which adaptation do you need to make in your daily life, as a result of the pituitary condition of your partner?
- Problems accepting?
- Crossing own limits

Relationship
When the physical appearance of your partner has changed, how does this affect you?
When your partner has physical complaints, hoe does this affect you?
When the personality of your partner has changed, how does this affect you?
When your partner suffers from mood changes, how does this affect you?
When your partner suffers from cognitive complaints, how does this affect you?
When your partner suffers from sleep problems, how does this affect you?
Is the balance in your relationship influenced by the pituitary condition?
When this is the case, how is it affected?
- Skewed relationship?

Do you have the feeling that you need to protect your partner? When this is the case, how does this affect you?
Do you feel supported by your partner?
Is the communication between you and your partner influenced as a result of the pituitary condition? When this is the case, how is it affected?
Do you encounter problems with a desire to have children?
Has sexuality/intimacy changed in your relationship, when yes how does this affect you?

Family
Does the pituitary condition of your partner influence your family? When this is the case how does it affect your family?
Do you feel supported by your family?

Social functioning
Do you feel supported by your social network?
Is the communication between you and your social network influenced as a result of the pituitary condition? When this is the case, how is it affected?
How does the pituitary condition of your partner affect your social life?
How does the pituitary condition of your partner affect your social network?

Employment
How does the pituitary condition of your partners affect your financial situation?
How does the pituitary condition of your partner affect your work?

Unmet needs (final questions)**:**
- Given all of this, what would you prefer to have known / to have had after receiving the diagnosis of your ill partner?
- What is your advice for someone who just received the diagnosis?

Finishing conversation:
Thank participants for their contribution

CHAPTER 13

The development and validation of the Leiden Bother and Needs Questionnaire for patients with Pituitary disease: the LBNQ-Pituitary

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ABSTRACT

Background: Patients report persisting impairment in Quality of Life (QoL) after treatment for pituitary disease. At present, there is no questionnaire to assess (a) whether patients with pituitary disease are bothered by these consequences, and (b) their needs for support.

Objective: To develop and validate a disease-specific questionnaire for patients with pituitary disease which incorporates patient perceived bother related to the consequences of the disease, and their needs for support.

Methods: Items for the Leiden Bother and Needs Questionnaire for patients with pituitary disease (LBNQ-Pituitary) were formulated based on results of a recent focus group study (n=49 items). 337 patients completed the LBNQ-Pituitary and six validated QoL questionnaires (EuroQoL-5D, SF-36, MFI-20, HADS, AcroQol, CushingQoL). Construct validity was examined by exploratory factor analysis. Reliabilities of the subscales were calculated with Cronbach's alphas, and concurrent validity was assessed by calculating Spearman's correlations between the LBNQ-Pituitary and the other measures.

Results: Factor analyses produced five subscales (i.e. Mood problems, Negative illness perceptions, Issues in sexual functioning, Physical and cognitive complaints, Issues in social functioning) containing a total of 26 items. All factors were found to be reliable (Cronbach's alphas all ≥.765), and the correlations between the dimensions of the LBNQ-Pituitary and other questionnaires (all P≤.0001) demonstrated convergent validity.

Conclusions: The LBNQ-Pituitary can be used to assess the degree to which patients are bothered by the consequences of the pituitary disease, as well as their needs for support. It could also facilitate an efficient assessment of patients' needs for support in clinical practice. We postulate that paying attention to needs for support will lead to optimal patient care (e.g. improvement in psychosocial care), and positively affect QoL.

INTRODUCTION

Pituitary adenomas can cause several symptoms in the physical, psychological, and social domain, and can be treated by surgery, drug treatment or additional radiotherapy. Symptoms can (partly) resolve upon treatment, but many patients will have permanent hypopituitarism and will require life-long multiple hormone replacement therapy and/or will experience remaining symptoms (1). In line with these findings, research in patients with pituitary diseases demonstrated that patients report Quality of Life (QoL) impairments (2), also after long-term remission (3-6). The increasing number of QoL studies in patients with pituitary disease suggests a growing interest in the patient's perspective (7). QoL in patients with pituitary disease has been mainly evaluated by generic QoL questionnaires assessing several domains, disease-specific QoL questionnaires assessing disease related QoL aspects, or domain-specific questionnaires assessing particular domain(s) of QoL. Disease-specific QoL questionnaires for pituitary diseases are available for Cushing's syndrome (i.e. CushingQoL, Tuebing CD-25 (8-10)), acromegaly (AcroQoL (11-13)) and growth-hormone deficiency (QoL-AGHDA (14)), whereas no questionnaires are available for patients with non-functioning pituitary adenoma or prolactinoma.

Recently, we performed a qualitative study utilizing focus group interviews in patients with pituitary diseases in order to further explore the patient's perspective on QoL (15). Issues raised in these conversations were compatible with items of available questionnaires, but other topics also emerged. New issues raised that are not covered in existing questionnaires were visual problems, fear of recurrence of the pituitary adenoma, problems with an altered personality, and lack of sympathy and understanding by others. Furthermore, patients reported unmet needs regarding care, such as dissatisfaction with other aspects of medical care i.e. psychological support (15). In contrast to the large number of studies measuring QoL in patients with pituitary disease, only few studies suggest strategies to improve QoL (7). Exploration of the patient's perspective is crucial in identifying potential unmet needs and aspects for improvement in QoL.

Therefore, the aim of the present study was to develop and validate a new questionnaire aiming to assess the degree to which patients are bothered by the consequences of their pituitary disease, as well as their needs for support. The patient's perspective elucidated during the focus group conversations (15) formed the basis for the development of this questionnaire.

PATIENTS AND METHODS

Patients

Patients between 18 and 80 years old with a pituitary disease (i.e. Cushing's disease (CD), acromegaly (ACRO), prolactinoma (PRL), and non-functioning adenoma (NFA)) monitored at our institute were invited by letter for this study (N=554). Those who did not respond were contacted by phone and encouraged to participate. A response was received from 408 patients (74%), but sixty-one of them (15%) denoted that they did not want to participate. Main reported reasons for not participating were language barrier or perceiving the questionnaire as being too time consuming. Eventually, 347 (63%) patients completed the questionnaires. Of these, 10 patients filled out less than 75% of the LBNQ-pituitary and were excluded from the analyses, resulting in a total number of 337 (61%) patients for inclusion. Clinical characteristics of patients were derived from medical records.

Diagnosis, treatment and follow-up

Details on diagnostic criteria and criteria for remission and follow-up have been previously described: CD (16), ACRO (3), PRL (5), NFA (17). Essentially, international guidelines for diagnosis, management were followed. At the time of the current study, all patients were in remission or well controlled with medical treatment regimens.

Procedure

All patients were asked to complete our newly developed questionnaire (see next paragraph), two generic QoL questionnaires and two domain-specific questionnaires. In addition, patients with CD or ACRO were also asked to fill out a disease-specific QoL questionnaire (CushingQoL or AcroQoL, respectively). Based on the preference of the patient, questionnaires were sent by email (online survey) or by regular mail, in order to increase response rate. 255 patients completed the questionnaire online, 82 patients by postal survey. Previous research demonstrated that paper-and-pencil and online surveys did not lead to different results (18). The Medical Ethical Committee of the LUMC approved this study.

Development of LBNQ-Pituitary

The items of the Leiden Bother and Needs Questionnaire for patients with Pituitary disease (LBNQ-Pituitary) were derived from recent focus group conversations (15). The format of the LBNQ-Pituitary was based on the "Belastungsfragebogen Parkinson kurzversion (BELA-P-k)" (Questionnaire on psychosocial Burden and Needs for help in Parkinson's disease) (19), which has been found to be valid and reliable for Dutch patients with Parkinson's disease (20).

Consequently, each item consists of three parts. Part A) a screening question to ask whether a certain complaint is present (Yes/To a certain extent/No). For some questions regarding fertility, their family or their partner, patients could also indicate "Not applicable".

Part B) a question on the extent by which the patients is bothered by the complaint (*Bothered by* (Bb)). Part C) a question to assess how much importance patients place on the attention form their healthcare provider for their complaint (*Needs for Support* (NfS)). Part B and C were scored on a 5-point Likert scale (0="not at all" to 4="extremely") and (0="not important" to 4="extremely important").

The initial LBNQ-Pituitary consisted of 49 items and one open-ended question (Supplement 1). To establish face validity, items were reviewed by experts from the field i.e., psychologists (MS, NGAK, AAK) and endocrinologists (NRB, AMP). In order to confirm the content and face validity (i.e. relevance, comprehensibility and acceptability of the items), cognitive debriefing interviews with 4 patients were conducted by the investigator (CDA).

Validated questionnaires to test concurrent validity

Generic QOL questionnaires:

EuroQoL-5D (EQ-5D) assesses the current health status reflected in five health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores are expressed on a 1-3 scale per dimension, with higher scores indicating worse QoL. The questionnaire also includes a visual analogue scale (VAS) ranging from 0 to 100 for recording an individual's rating of their current health-related well-being, with higher scores indicating a better health status. The EQ-5D was found to be reliable and valid (21).

MOS Short Form 36 (SF-36) assesses functional status and general well-being during the previous month. The items cover nine health concepts: 1) physical functioning, 2) social functioning, 3) role limitation (physical), 4) role limitation (emotional), 5) mental health, 6) vitality, 7) pain, 8) general health perception, and 9) general perception of change in health. Scores are expressed on a 0–100 scale, and higher scores indicate a better QoL. The SF-36 has been found to be reliable and valid (22;23).

Domain-specific QoL questionnaires:

Multidimensional Fatigue Inventory (MFI-20) assesses fatigue, using a five-point scale. Five different dimensions can be calculated: 1) General fatigue, 2) Physical fatigue, 3) Reduced activity, 4) Reduced motivation, and 5) Mental fatigue. Scores vary from 0-20; with higher scores indicating greater fatigue. The MFI-20 yields adequate levels of reliability and validity (24).

Hospital Anxiety and Depression Scale (HADS) assesses anxiety and depressive symptoms and consists of 14 items on a 4-point scale, and both anxiety (7 items) and depression (7 items) scores range from 0-21 points. Higher scores indicate more severe anxiety and/or depressive symptoms. A score >8 points on one of the subscales is being used to indicate patients as being anxious or depressed respectively (25). The HADS yields adequate levels of reliability and validity (26;27).

Disease-specific QoL questionnaires:

AcroQoL assesses acromegaly-related QoL and consists of 22 questions on a five-point scale. Three different dimensions can be calculated: 1) Physical score, 2) Psychological-appearance, 3) Psychological-personal relations, and a total score. Lower scores indicate worse QoL. The AcroQoL was found to be reliable and valid (11-13).

CushingQoL assesses Cushing-related QoL and consists of 12 questions on a five-point scale. The total score ranges from 12 to 60, with a lower score indicating worse QoL. The CushingQoL yields adequate levels of reliability and validity (10;28).

Statistics

In order to assess the construct validity of the LBNQ-Pituitary, an exploratory factor analysis was performed on all items using the *Bothered by* (Bb) scores (n = 49). We conducted exploratory factor analysis using oblique rotation. To check for multicollinearity the correlation matrix was studied. The Kaiser-Meyer-Olkin (KMO) measure was used to test for sampling adequacy. KMO can range from 0 to 1, with values near 0 indicating diffusion in the pattern of correlations, and values near 1 indicating compact patterns of correlation. Internal consistency of the LBNQ-Pituitary dimensions was measured using Cronbach's alpha coefficients.

To establish concurrent validity correlations between Bb scores and scores on the other questionnaires were calculated. Pearson's correlations were calculated when data were normally distributed and Spearman's correlations were calculated when data were not normally distributed. Correlation coefficients ranging from .10 to .30 indicate a small effect, .30 to .50 a medium effect, and >.50 a large effect. It was expected that scales that are conceptually related correlate moderately to highly with one another (convergent validity). Conversely, scales with a less clear or absent conceptual relation are expected to show weak correlations (divergent validity). In order to correct for multiple testing the Bonferroni correction was applied and the level of significance was set at $P \leq .0001$.

Discriminant validity was examined by LBNQ-Pituitary scores between the different pituitary diseases and by using the HADS cut-off points (score>8 points). For the comparison between pituitary diseases an ANOVA was used when data were normally distributed and a Kruskal Wallis Test was used when data were not normally distributed. For the comparison between patients being clinically anxious or depressed, independent sample t-tests were used when data were normally distributed, and Mann-Whitney U tests when data were not normally distributed. The level of significance was set at $P<.05$.

RESULTS

Cognitive debriefing interviews

The LBNQ-Pituitary was completed by four patients in the presence of the investigator (CDA) (3 men and 1 woman; mean age: 57.5±18.7 years). Patients were asked to fill-out the questionnaire and were asked about their thoughts about the questions and whether they thought items were missing. Patients agreed with the items and found it relevant that attention was being paid to the psychosocial consequences of their disease. The LBNQ-Pituitary proved to be feasible and there were no cues for missing items. Only question 49 ('As a consequence of my pituitary condition, I experience difficulties in performing my work') was adapted by adding the answer option 'Not applicable'.

Patient characteristics (Table 1)

The full survey was completed by 337 patients (61% females). The mean age of patients was 56.8±13.7 years with a mean duration since diagnosis of 15.3±11.4 years.

Table 1. Patient characteristics

	Total (n=337)	**CD (n=72)***	**ACRO (n=76)**	**PRL (n=92)**	**NFA (n=97)**
Gender (M/F)	131/206	16/56	38/38	23/69	54/43
Age (yrs)	56.8 (13.7)	54.5 (12.6)	60.6 (13.1)	50.7 (13.3)	61.3 (13.0)
Education, n (%)					
Low	108 (32%)	25 (35%)	33 (43%)	22 (24%)	28 (29%)
Medium	97 (29%)	20 (28%)	21 (28%)	27 (29%)	29 (30%)
High	132 (39%)	27 (37%)	22 (29%)	43 (47%)	40 (41%)
Marital status, n (%)					
Single	43 (13%)	11 (15%)	7 (9%)	15 (16%)	10 (10%)
Relationship/marriage	262 (78%)	52 (72%)	62 (82%)	68 (75%)	80 (83%)
Divorced	17 (5%)	7 (10%)	3 (4%)	5 (5%)	2 (2%)
Widow	15 (4%)	2 (3%)	4 (5%)	4 4%)	5 (5%)
Pituitary surgery, n (%)	228 (68%)	53 (74%)	68 (90%)	26 (28%)	81 (84%)
Radiotherapy, n (%)	76 (23%)	22 (31%)	19 (25%)	10 (11%)	25 (26%)
Duration of follow-up (yrs)	15.3 (11.4)	16.2 (13.6)	18.7 (10.6)	16.1 (10.5)	11.3 (10.1)
Medical treatment for the pituitary disease#	231 (69%)	49 (68%)	52 (68%)	61 (66%)	69 (71%)

*21 patients were diagnosed with adrenal Cushing's syndrome, of whom 12 were treated with bilateral adrenalectomy and 10 were treated with unilateral adrenalectomy. # hormonal replacement therapy and/or suppressant medication. CD: Cushing's disease; ACRO: acromegaly; PRL: prolactinoma; NFA: non-functioning pituitary adenoma.

Frequency of reported Bother and Needs for Support (Table 2)

The number of patients who reported to be bothered by a certain complaint (i.e. "This problem and its consequences bother me:" *3. Considerably or 4. Extremely*) were counted, as well as the number of patients who reported a need for support for a certain complaint (i.e. "I find attention from my healthcare providers to be:" *3. Considerably important or 4. Extremely important*). Among the most bothersome complaints, fatigue was mentioned by 63 patients (17%), while a larger group reported need for support regarding fatigue from their healthcare providers (25%).

Table 2. Top-10 highest Bothers and Needs for Support

Highest Bothered by (Bb)	n (%)	Highest Needs for Support (NfS)	n (%)
Fatigue	63 (17%)	Fatigue	84 (25%)
Difficulties in performing work	42 (12%)	Afraid that pituitary tumour will recur	68 (20%)
Problems concentrating	37 (11%)	Worried about physical symptoms	65 (19%)
More sensitive to stressful situations	35 (10%)	Problems concentrating	62 (18%)
Pain	35 (10%)	Less interested in sex	55 (16%)
Going beyond own limits	34 (10%)	Mood swings	55 (16%)
Less interested in sex	34 (10%)	Memory problems	54 (16%)
Physical problems during sex	34 (10%)	Difficulties in performing work	52 (15%)
Sleeping problems	34 (10%)	More sensitive to stressful situations	51 (15%)
Difficulties letting go of certain thoughts	33 (10%)	Sleeping problems	50 (15%)

Construct validity and reliability analysis (Table 3)

Of the initial 49 items, after factor analyses 26 items remained (see Supplement 2 for a detailed description). A factor structure with five factors with eigenvalues over Kaiser's criterion 1 and a total explained variance of 58.5% fitted the data best. The KMO measure of sampling adequacy was 0.94 indicating adequate fit for factor analysis (i.e. the data are likely to factor well) (29). Cronbach alpha's were calculated for each factor, and all factors were found to be reliable (Cronbach's alpha .765, or higher).

All items that fell out during factor analyses were inspected (n=23). Some items appeared to be of interest only for a subset of subjects, for instance, 'Deteriorated partner relationship', 'Worries not being able to have children' and 'Feeling to fail in care for family' and were kept as optional items for these subjects. Furthermore, some items appeared rather disease specific, and of significant interest for the respective diseases; 'Difficulties letting go of certain thoughts', 'Jealousy', 'Trouble accepting', 'Sleeping problems', 'Sadness' and 'Shame' were more relevant to patients with CD, whereas 'Negative thoughts about medication' turned out to be more relevant to patients with PRL, and 'Impaired eyesight' more relevant to patients with NFA. Therefore, these items (n=8) were retained in the questionnaire and added as optional questions for patients with CD, PRL or NFA. The sum scores of the subscales were

Table 3. Results final factor analysis: factor loadings in bold

Item (item nr)	Mood problems	Negative illness perceptions	Issues in sexual functioning	Physical & Cognitive complaints	Issues in social functioning
More easily irritated (20)	**.780**	.058	.097	-.074	.034
Changes in personality (18)	**.595**	-.137	.098	-.091	.120
Emotional reactions have changed (19)	**.585**	-.011	.027	-.219	.049
Mood swings (12)	**.584**	-.128	.091	-.125	.022
Anger (23)	**.491**	-.220	-.033	.056	.227
Panic (13)	**.319**	-.078	-.079	-.204	.224
Negative thoughts about how condition will progress (37)	-.028	**-.809**	-.018	-.040	.081
Negative thoughts about the extent to which the condition can be kept under control (38)	-.109	**-.756**	.043	-.029	.163
Negative thoughts about the consequences of the condition (36)	.135	**-.678**	-.050	-.027	.054
Worried about physical symptoms (16)	.218	**-.537**	.070	-.168	-.021
Afraid that pituitary tumour will recur (17)	.240	**-.438**	.159	.089	-.004
Less interested in sex (41)	.010	.040	**.822**	-.063	-.056
Physical problems during sex (40)	-.017	.017	**.783**	.018	.114
Guilt towards partner/close family (26)	.200	-.170	**.305**	-.051	.193
Problems concentrating (6)	.079	.066	.010	**-.766**	.097
Memory problems (8)	.114	.152	-.010	**-.704**	.127
Fatigue (1)	-.023	-.108	.185	**-.694**	-.096
Difficulties in doing several things at the same time (7)	.076	.015	.048	**-.644**	.137
Pain (2)	-.134	-.365	.028	**-.501**	.022
Going beyond own limits (33)	.167	-.135	.052	**-.461**	-.003
Changes in physical appearance (3)	.093	-.174	.052	**-.358**	.036
Circle of friends has become smaller (45)	-.127	-.017	.085	.027	**.847**
Loneliness (25)	.195	-.051	-.087	-.110	**.682**
Feeling uncomfortable in social situations (46)	.058	-.073	.046	.001	**.620**
Lack of understanding of the consequences of the condition from people in social circle (47)	.074	-.028	.025	-.130	**.548**
Feeling the need to be alone (30)	.260	-.038	.089	-.092	**.421**
Cronbach alfa	**.889**	**.861**	**.765**	**.876**	**.862**

α: Cronbach's alpha coefficient.

all transformed to a 0-100 scale. The final LBNQ-Pituitary consisted of 26 items, which can be extended by three optional items being relevant for a subset of patients and eight optional items being relevant for a specific pituitary condition. For an overview of retained items see Supplement 3.

Concurrent validity (Table 4)

As expected, a higher Bb score on Mood problems was strongly associated with worse mood on the EQ-5D, as well as with more anxiety and more depressive symptoms (HADS) (convergent validity). On the other hand, a higher Bb score on Mood problems was also strongly associated with more impairment in social functioning (SF-36) (less divergent validity). Furthermore, in patients with CD a higher Bb on Mood problems was strongly associated with worse disease-specific QoL.

A higher Bb score on Negative illness perceptions was strongly associated with more impairment in social functioning (SF-36), more anxiety and a higher total score on the HADS. In patients with CD a higher Bb score on Negative illness perceptions was strongly associated with worse disease-specific QoL.

A higher Bb score on Issues in sexual functioning was associated with more impairment in disease-specific QoL in patients with CD and in patients with ACRO (i.e. AcroQoL, except subscale Psychological appearance).

As expected, a higher Bb score on Physical and Cognitive complaints was strongly correlated with more impairments in the performance of daily activities (EQ-5D), worse general well-being (VAS EQ-5D), more impairments in physical functioning, more physical role limitations, and more pain (SF-36) (convergent validity). On the other hand, a higher Bb score on Physical and Cognitive complaints was also strongly associated with more impairment in social functioning, more emotional role limitations (SF-36), more anxiety and more depressive symptoms (HADS) (less divergent validity). In addition, it was associated with worse disease-specific QoL in patients with CD and in patients with ACRO (i.e. AcroQoL Physical score and Total score) (convergent validity), whereas no significant correlations were found with the AcroQoL subscales Psychological-appearance and Psychological-personal relations (divergent validity).

As expected, a higher Bb score on Issues in social functioning was strongly associated with more impairment in social functioning (SF-36) (convergent validity), whereas also high associations were found with physical and emotional role limitations (SF-36). Furthermore, a higher Bb score on Issues in social functioning was highly associated with more depressive symptoms and a higher total score on the HADS (less divergent validity). In addition, it was associated with worse disease-specific QoL in patients with CD and patients with ACRO (i.e. AcroQoL all subscales).

Finally, a higher total Bb score was strongly associated with more impairment in daily activities, worse mood (EQ-5D), worse general well-being (VAS EQ-5D), more impairment in social

Table 4. Significant correlations between Bothered by scores on the subscales of the LBNQ-Pituitary and QoL measures

	Mood problems	Negative illness perceptions	Issues in sexual functioning	Physical & Cognitive complaints	Issues in social functioning	Total Bb
EQ-5D						
Mobility		.261		.297	.236	.275
Selfcare				.232	.214	.221
Daily activity	.387	.459	.304	**.547**	.449	**.534**
Pain	.302	.369		.480	.337	.421
Mood	.499	.440	.340	.422	.427	**.501**
VAS (well-being)	-.496	-.482	-.335	**-.596**	-.413	**-.599**
SF-36						
Physical functioing	-.358	-.433	-.244	**-.518**	-.418	-.483
Social functioing	**-.599**	**-.534**	-.414	**-.629**	**-.662**	**-.690**
Role limitations Physical	-.457	-.489	-.329	**-.639**	**-.530**	**-.611**
Role limitations Emotional	-.492	-.406	-.328	**-.569**	**-.531**	**-.561**
Mental Health	-.247	-.209				-.220
Vitality	-.252			-.289		-.264
Pain	-.372	-.432	-.240	**-.559**	-.436	**-.505**
General Health		-.220		-.257		-.248
Health change						
MFI-20						
General fatigue						
Physical fatigue						
Reduced activity						
Reduced motivation		-.220		-.245	-.220	-.265
Mental fatigue						
HADS						
Anxiety	**.598**	**.552**	.389	**.530**	.471	**.612**
Depression	**.576**	.493	.458	**.632**	**.565**	**.670**
Total score	**.659**	**.572**	.469	**.649**	**.573**	**.716**
CushingQoL	**-.696**	**-.661**	**-.675**	**-.873**	**-.802**	**-.884**
AcroQoL						
Physical score			**-.513**	**-.705**	**-.586**	**-.661**
Psychological-appearance					**-.509**	
Psychological-personal relations			**-.593**		**-.525**	**-.563**
Total score			**-.533**	**-.575**	**-.644**	**-.613**

All Spearman's correlations, P ≤ .0001. Empty cells: correlation was not significant. Bold: correlations ($r \geq .500$).

functioning, more physical and emotional role limitations, and more pain (SF-36). Likewise, a higher total Bb score was associated with more anxiety and more depressive symptoms (HADS). In addition, a higher Bb total score was associated with worse disease-specific QoL in patients with CD and patients with ACRO (i.e. AcroQoL, except subscale Psychological appearance).

Discriminant validity

Between different pituitary diseases

Patients with CD reported a higher Bb and NfS score on Physical and Cognitive complaints compared to the other groups (ACRO, PRL, NFA) (P=.004 and P=.043, respectively). Furthermore, patients with CD reported a higher Bb score on Issues in Social functioning, as well as a higher Bb Total score compared to patients with PRL (P=.004 and P=.023, respectively). In addition, patients with CD reported a higher NfS score on Issues in Social functioning, as well as Total NfS compared to patients with ACRO (P=.012 and P=.034, respectively) (Supplement 4). On all other subscales of the LNBQ-Pituitary no significant differences were found, pointing to a considerable overlap in perceived consequences between pituitary diseases.

Cut-off scores HADS (Figure 1a-b)

Based on the clinically used cut-off score of the HADS it was observed that 47 patients (14%) were clinically anxious and 45 (13%) were clinically depressed. Based on this observation, groups were formed (anxious vs. not anxious; depressed vs. not depressed) and the scores on the Bb subscales of the LBNQ-Pituitary were compared between groups. It was found that patients who could be classified as anxious and/or depressed (>8 points on HADS subscales respectively) showed higher scores on all Bb subscales, as well as the Bb Total score (P≤.0001).

DISCUSSION

The present study demonstrated that the resultant factors derived from the exploratory factor analysis of the *Bothered by* (Bb) items of the LBNQ-Pituitary were in accordance with the themes discussed in the focus group conversations i.e. mood problems, negative illness perceptions, issues in sexual functioning, physical and cognitive complaints, and issues in social functioning (15). Internal consistency of these underlying dimensions was supported by high Cronbach's alphas. Convergent validity was observed for the subscales Mood problems, Physical and Cognitive complaints and Issues in social functioning. Although divergent validity was also observed by no or weaker correlations with incongruous subscales, some strong correlations were observed between these LBNQ-Pituitary subscales and non-corresponding subscales, such as the strong correlation between Bb subscale Mood problems and Social functioning (SF-36). Furthermore, the LBNQ-Pituitary showed good discriminant validity

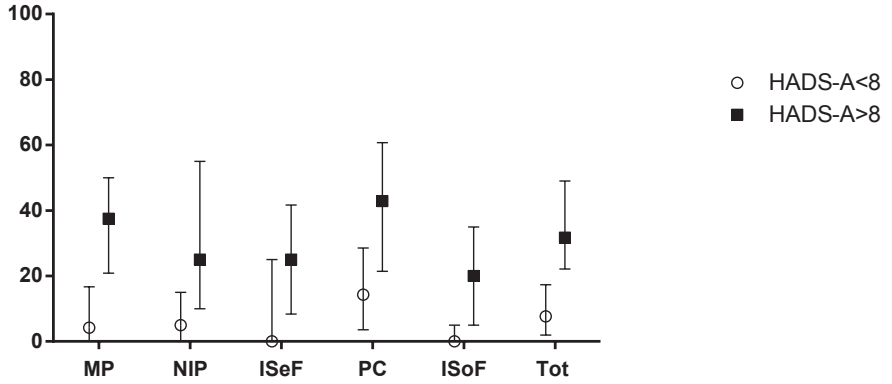

Figure 1a. Bothered by scores of patients with vs. without anxiety

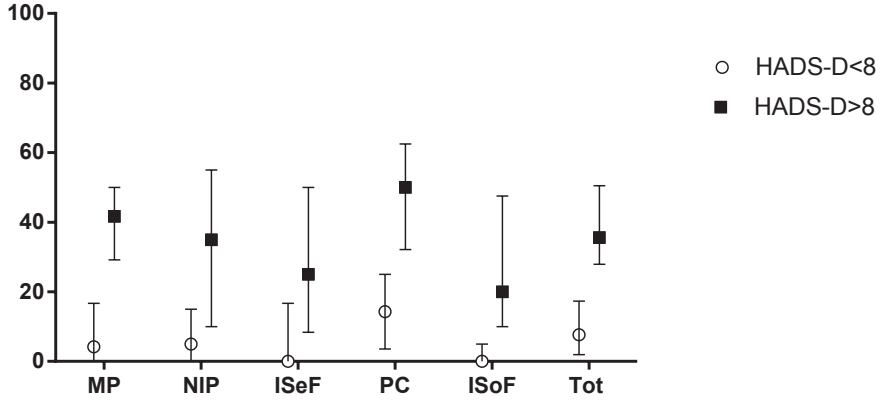

Figure 1b. Bothered by scores of patients with vs. without depression.
Median and inter quartile range (IQR). HADS-A: Anxiety subscale of the Hospital Anxiety and Depression Scale. HADS-D: Depression subscale of the Hospital Anxiety and Depression Scale. MP: Mood Problems, NIP: Negative Illness Perceptions, ISeF: Issues in Sexual Functioning, PC: Physical and Cognitive complaints, ISoF: Issues in Social Functioning, Tot: Total score.

between patients with various pituitary disease (e.g. patients with CD reported a higher score on all Bb and NfS subscales compared to the other groups) and between patients being anxious or depressed as determined by the scores on the HADS.

Based on the results of our recent focus group study (15) it was assumed that physical and cognitive complaints would be identified as two separate dimensions. Surprisingly, in the present study physical complaints and cognitive complaints both loaded on one factor. A possible explanation might be that the question assessing fatigue was not explicitly divided into physical fatigue and mental fatigue. We speculate that specifying this item in future research, might result in fatigue being represented in two factors.

The subscale Negative illness perceptions showed strong correlations with social functioning (SF-36) and anxiety (HADS). These correlations could be explained by previous literature

showing that illness perceptions contribute to QoL in patients with pituitary disease (30;31), and in other patient populations (32;33). Furthermore, the subscale Issues in sexual functioning showed strong correlations with disease-specific QoL (i.e. CushingQoL, AcroQoL), whereas only small to moderate associations were found with generic QoL measures. This is probably explained by the fact that both disease-specific QoL measures include items about sexuality, whereas the generic measures do not assess sexuality. This observation points to convergent validity of this subscale. Furthermore, it could be observed that scores on the LBNQ-Pituitary correlate highly with outcomes on the disease-specific questionnaires, which supports the convergent validity in terms of disease specificity.

The observation that strong correlations were observed between incongruous subscales, could possibly be explained by the tight connections between the domains of the biopsychosocial model (34), such as that mood problems might also result in less social functioning. Surprisingly, the LBNQ-Pituitary showed only weak correlations with the Multidimensional Fatigue Inventory-20. This might also be explained by the fact that fatigue was assessed with just one item in the present version of the LBNQ-Pituitary.

Furthermore, the disease-specific burden of pituitary adenomas observed in this study is in accordance with previous literature, with patients with CD reporting the largest negative impact on QoL (7;35;36). The LBNQ-Pituitary offers the possibility to assess bother and needs for support in people with pituitary disease in general with potential comorbid hypopituitarism, while it can also be used to assess aspects related to specific pituitary disease, such as CD or PRL. Moreover, since there are no questionnaires available for patients with NFA or PRL, the LBNQ-Pituitary can be used in these patient groups.

To the best of our knowledge, no work has been published reporting a similar questionnaire to the LBNQ-Pituitary which can assess to which extent patients are bothered by consequences of the disease, as well as their needs for support. We postulate that this questionnaire will provide valuable information, in addition to already available QoL data, which is needed for the improvement of psychosocial care in patients with pituitary disease. Furthermore, the LBNQ-Pituitary can be used by clinicians to distinguish between specific bothers and/or specific needs for support. Awareness of patients' needs for support could facilitate the translation from patients' needs to optimal patient care. For an overview of the distribution of reported needs for support in our cohort, see Figure 2. Considering the fact that unmet needs are found to influence QoL (37), and that patients with pituitary disease previously reported unmet needs (e.g. "better cooperation and communication between medical specialties", "absence of recognition for certain complaints") (15), we postulate that paying attention to patients' needs for support will positively affect QoL.

In conclusion, the LBNQ-Pituitary can be used to assess whether patients are bothered by the consequences of the disease, as well as their needs for support. Nevertheless, future research is needed to further establish the psychometric properties, for instance by the use of a confirmatory factory analysis in another cohort in the Netherlands, but also in patients

from a different country and with a different language. The LBNQ-Pituitary can be used in clinical research (e.g. to compare bother and needs for support between groups, to evaluate the effect of interventions regarding bother and needs). It can also be used to facilitate the efficient assessment of bother and needs for support in patients with pituitary disease in clinical practice, and further research into this area is warranted.

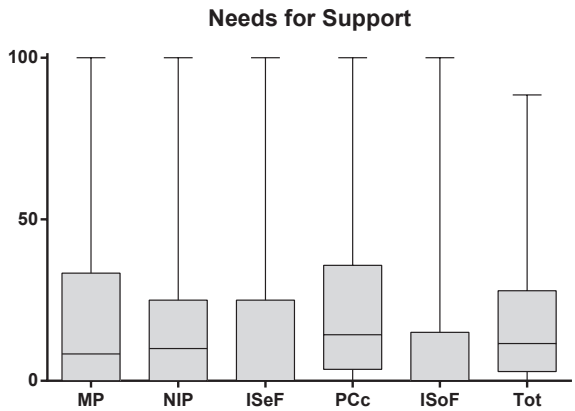

Figure 2. Needs for Support.
Distribution of Needs for Support (range 0-100), with a higher score indicating a greater need for support. MP: Mood Problems, NIP: Negative Illness Perceptions, ISeF: Issues in Sexual Functioning, PC: Physical and Cognitive complaints, ISoF: Issues in Social Functioning, Tot: Total score.

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SUPPLEMENT 1A. FORMAT OF THE LBNQ-PITUITARY

1. As a consequence of my pituitary condition, I experience **fatigue**.

a. YES / To a certain extent / NO (*If NO, please proceed to the next question*)

b. This problem and its consequences bother me.

☐ Not at all ☐ Slightly ☐ Moderately ☐ Considerably ☐ Extremely

c. I find attention for this problem from my healthcare providers to be

☐	☐	☐	☐	☐
Not important	Slightly important	Moderately important	Considerably important	Extremely important

SUPPLEMENT 1B. OVERVIEW OF INITIAL ITEMS*

1. As a consequence of my pituitary condition, I experience **fatigue.**
2. As a consequence of my pituitary condition, I experience **physical pain.**
3. As a consequence of my pituitary condition, I experience **changes in my physical appearance.**
4. As a consequence of my pituitary condition, I experience **impaired eyesight.**
5. As a consequence of my pituitary condition, I experience **sleeping problems**.
6. As a consequence of my pituitary condition, I experience **problems concentrating**.
7. As a consequence of my pituitary condition, I experience **difficulties in doing several things at the same time.**
8. As a consequence of my pituitary condition, I experience **memory problems**.
9. As a consequence of my pituitary condition, I experience **difficulties letting go of certain thoughts.**
10. As a consequence of my pituitary condition, I **feel down.**
11. As a consequence of my pituitary condition, I experience **anxiety.**
12. As a consequence of my pituitary condition, I experience **mood swings.**
13. As a consequence of my pituitary condition, I have **a tendency to panic in certain situations.**
14. As a consequence of my pituitary condition, I am **more sensitive to stressful situations than before.**
15. As a consequence of my pituitary condition, **I am afraid to faint in certain situations.**
16. As a consequence of my pituitary condition, **I am worried about physical symptoms.**
17. I am **afraid** that the pituitary tumour will recur.
18. As a consequence of my pituitary condition, I experience **changes in my personality.**
19. As a consequence of my pituitary condition, **my emotional reactions have changed.**

20. As a consequence of my pituitary condition, I am **more easily irritated than before.**
21. As a consequence of my pituitary condition, **my confidence has decreased.**
22. As a consequence of my pituitary condition, I experience **shame.**
23. As a consequence of my pituitary condition, I experience **anger.**
24. As a consequence of my pituitary condition, I experience **sadness.**
25. As a consequence of my pituitary condition, I experience **loneliness.**
26. As a consequence of my pituitary condition, I experience **guilt towards my partner/ close family.**
27. As a consequence of my pituitary condition, I experience **frustration.**
28. As a consequence of my pituitary condition, **I experience tension.**
29. As a consequence of my pituitary condition, I experience **jealousy towards other (healthy) people.**
30. As a consequence of my pituitary condition, I **sometimes feel the need to be alone for a while.**
31. As a result of my pituitary condition, **I drink more alcohol than previously.**
32. I have **trouble accepting** my pituitary condition and its consequences.
33. I do more than is actually good for me (I go beyond my own limits).
34. I think that every (new) symptom is related to my pituitary condition.
35. I often brood on the **causes** of my pituitary condition.
36. I have negative thoughts about the **consequences** of my pituitary condition.
37. I have negative thoughts about how my pituitary condition will progress.
38. I have negative thoughts about the extent to which my pituitary condition can be kept under **control**.
39. I have **negative thoughts about the medication** I take for my pituitary condition.
40. As a consequence of my pituitary condition, I experience **physical problems during sex.**
41. As a consequence of my pituitary condition, I am **less interested in sex.**
42. As a consequence of my pituitary condition, **I worry that I will not be able to have children.**
43. As a consequence of my pituitary condition, I **feel that I am failing to adequately care for my family.**
44. As a consequence of my pituitary condition, **the relationship with my partner has deteriorated.**
45. As a consequence of my pituitary condition, **my circle of friends has become smaller.**
46. As a consequence of my pituitary condition, **I feel uncomfortable in social situations.**
47. I experience a **lack of understanding of the consequences of my pituitary condition from the people in my social circle.**
48. As a consequence of my pituitary condition, I experience **limitations in engaging in my hobbies.**

49. As a consequence of my pituitary condition, I experience **difficulties in performing my work.**
50. Other problems that I experience: ... (Please also indicate whether you need attention for or coaching in dealing with these problems)

*The Dutch items of the LBNQ-Pituitary were translated by using a forward-backward method i.e., items were first translated into English, and then the English items were translated back into Dutch. Discrepancies were discussed. Then the English items of the LBNQ-Pituitary were presented to seven native English patients being monitored at the department of diabetes and Endocrinology of the University College London Hospital (UK).

SUPPLEMENT 2. DESCRIPTION OF FACTOR ANALYSES

The first factor analysis was conducted on the initial 49 items. Ten factors had eigenvalues over Kaiser's criterion of 1 and in combination explained 59.8% of the variance. Items with initial statistics (communalities) <0.30 were excluded (n=8: Difficulties letting go of certain thoughts (9), Negative thoughts about medication (39), Jealousy (29), Limitations in engaging hobbies (48), Deteriorated partner relationship (44), Every (new) symptom being related to condition (34), Sadness (24), Trouble accepting (32)). After excluding these variables, we re-ran the factory analysis.

This second factor analysis was conducted on 41 items. Nine factors had eigenvalues over Kaiser's criterion of 1 and in combination explained 59.9% of the variance. Items with initial statistics (communalities) <0.30 were excluded (n=4: Feeling down (10), difficulties performing work (49), afraid to faint in certain situations (15), drinking more alcohol than previously (31)). After excluding these variables, we re-ran the factory analysis.

This third factor analysis conducted on the 37 items, indicated eight factors with eigenvalues over Kaiser's criterion of 1 and in combination explained 60.7% of the variance. Items with initial statistics (communalities) <0.30 were excluded (n=1: Worries not being able to have children (42)). After excluding this variable, we re-ran the factory analysis.

The fourth factor analysis on 36 items indicated seven factors with eigenvalues over Kaiser's criterion of 1 and in combination explained 60.8% of the variance. Items with initial statistics (communalities) <0.30 were excluded (n=2: Feeling to fail in care for family (43), Impaired eyesight (4)). After excluding these variables, we re-ran the factory analysis.

This fifth factor analysis on 34 items indicated seven factors with eigenvalues over Kaiser's criterion of 1 and in combination explained 62.7% of the variance. Items which loaded on more than one factor and with differences in factor loadings <.05 were excluded from the analysis (n=2: Frustration (27), Sleeping problems (5)). After excluding these variables, we re-ran the factory analysis.

This sixth factor analysis on 32 items indicated six factors with eigenvalues over Kaiser's criterion of 1 and in combination explained 61.0% of the variance. Items which loaded on more than one factor and with differences in factor loadings <.05 were excluded from the analysis (n=1: Brood on causes of condition (35)). After excluding this variable, we re-ran the factory analysis.

This seventh factor analysis on 31 items indicated six factors with eigenvalues over Kaiser's criterion of 1 and in combination explained 61.6% of the variance. Items which loaded on more than one factor and with differences in factor loadings <.05 were excluded from the analysis (n=1: More sensitive to stressful situations than before (14)). After excluding this variable, we re-ran the factory analysis.

This eighth factor analysis on 30 items indicated six factors with eigenvalues over Kaiser's criterion of 1 and in combination explained 61.6% of the variance. Items which loaded on more than one factor and with differences in factor loadings <.05 were excluded from the analysis (n=1: Shame (22)). After excluding this variable, we re-ran the factory analysis.

This ninth factor analysis on 29 items indicated six factors with eigenvalues over Kaiser's criterion of 1 and in combination explained 61.1% of the variance. Items which loaded on more than one factor and with differences in factor loadings <.05 were excluded from the analysis (n=1: Tension (28)). After excluding this variable, we re-ran the factory analysis.

This tenth factor analysis on 28 items indicated five factors with eigenvalues over Kaiser's criterion of 1 and in combination explained 58.3% of the variance. Items which loaded on more than one factor and with differences in factor loadings <.05 were excluded from the analysis (n=1: Confidence has decreased (21)). After excluding this variable, we re-ran the factory analysis.

This eleventh factor analysis on 27 items indicated five factors with eigenvalues over Kaiser's criterion of 1 and in combination explained 58.2% of the variance. Items which loaded on more than one factor and with differences in factor loadings <.05 were excluded from the analysis (n=1: Anxiety (11)). After excluding this variable, we re-ran the factory analysis.

The twelfth and final factor analysis on 26 items indicated five factors with eigenvalues over Kaiser's criterion of 1 and in combination explained 58.5% of the variance. Kaiser-Meyer-Olkin (KMO) measure was 0.94 ('superb'), indicating adequate sample size (29). These five factors were retained in the final analysis. Cronbach's α were calculated for each factor, and all factors were found to be reliable (> .765).

SUPPLEMENT 3. ITEMS RETAINED IN THE LBNQ-PITUITARY

Subscale	Item (item nr.)
1. Mood problems	More easily irritated (20)
	Changes in personality (18)
	Emotional reactions have changed (19)
	Mood swings (12)
	Anger (23)
	Panic (13)
2. Negative illness perceptions	Negative thoughts about how condition will progress (37)
	Negative thoughts about the extent to which the condition can be kept under control (38)
	Negative thoughts about the consequences of the condition (36)
	Worried about physical symptoms (16)
	Afraid that pituitary tumour will recur (17)
3. Issues in sexual functioning	Less interested in sex (41)
	Physical problems during sex (40)
	Guilt towards partner/close family (26)
4. Physical & cognitive complaints	Problems concentrating (6)
	Memory problems (8)
	Fatigue (1)
	Difficulties in doing several things at the same time (7)
	Pain (2)
	Going beyond own limits (33)
	Changes in physical appearance (3)
5. Issues in social functioning	Circle of friends has become smaller (45)
	Loneliness (25)
	Feeling uncomfortable in social situations (46)
	Lack of understanding of the consequences of the condition from people in social circle (47)
	Feeling the need to be alone (30)
Relevant for a subset of patients	Worries not being able to have children (42)
	Feeling to fail in care for family (43)
	Deteriorated partner relationship (44)
Additional items CD	Difficulties letting go of certain thoughts (9)
	Jealousy (29)
	Troubles with acceptance (32)
	Sleep problems (5)
	Sadness (24)
	Shame (22)
Additional items PRL	Negative thoughts about medication (39)
Additional items NFA	Impaired eyesight (4)

SUPPLEMENT 4. BOTHER AND NEEDS FOR SUPPORT BETWEEN DIFFERENT PITUITARY ADENOMAS

	CD (n=72)*	ACRO (n=76)	PRL (n=92)	NFA (n=97)	P value
Bothered by					
Mood problems	12.5 (0.0-29.2)	4.2 (0.0-12.5)	6.3 (0.0-29.2)	4.2 (0.0-25.0)	.169
Negative illness perceptions	10.0 (5.0-20.0)	5.0 (0.0-15.0)	5.0 (0.0-18.8)	5.0 (0.0-20.0)	.118
Issues in sexual functioning	8.3 (0.0-25.0)	0.0 (0.0-25.0)	8.3 (0.0-25.0)	0.0 (0.0-25.0)	.313
Physical and Cognitive complaints	25.0 (8.0-46.4)[b, c, d]	16.1 (4.5-34.8)[a]	14.3 (3.6-25.0)[a]	10.7 (3.6-30.4)[a]	**.004**
Issues in Social functioning	5.0 (0.0-20.0)[b]	0.0 (0.0-5.0)	0.0 (0.0-10.0)[a]	0.0 (0.0-5.0)	**.004**
Total bothered by	15.4 (7.7-29.8)[b]	7.7 (2.9-17.3)	10.6 (1.2-19.7)[a]	7.7 (2.3-22.1)	**.023**
Needs for Support					
Mood problems	12.5 (0.0-41.7)	4.2 (0.0-16.7)	8.3 (0.0-36.5)	8.3 (0.0-29.2)	.163
Negative illness perceptions	15.0 (5.0-25.0)	10.0 (0.0-20.0)	10.0 (0.0-23.8)	10.0 (0.0-30.0)	.072
Issues in sexual functioning	8.3 (0.0-25.0)	0.0 (0.0-25.0)	0.0 (0.0-33.3)	0.0 (0.0-25.0)	.364
Physical and Cognitive complaints	25.0 (4.5-56.3)[b, c, d]	14.3 (3.6-31.3)[a]	14.3 (0.0-32.1)[a]	14.3 (0.0-32.1)[a]	**.043**
Issues in Social functioning	5.0 (0.0-23.8)[d]	0.0 (0.0-5.0)[a]	0.0 (0.0-10.0)	0.0 (0.0-10.0)	**.012**
Total Needs for Support	20.2 (6.0-32.5)[d]	8.7 (1.9-19.2)[a]	11.1 (1.0-27.9)	8.7 (3.4-24.5)	**.034**

Data is presented as median and inter quartile range (IQR). Non-parametric Kruskal Wallis Test, *P*<.05.
*21 patients were diagnosed with adrenal Cushing's syndrome, of whom 12 were treated with bilateral adrenalectomy and 10 were treated with unilateral adrenalectomy. CD: Cushing's disease; ACRO: acromegaly; PRL: prolactinoma; NFA: non-functioning pituitary adenoma. [a]compared to CD, [b]compared to PRL, [c]compared to NFA, [d]compared to ACRO.

CHAPTER 14

Enhanced self-efficacy after a self-management programme in pituitary disease: a randomized-controlled trial

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ABSTRACT

Context: Patients with pituitary disease report impairments in Quality of Life (QoL) despite optimal biomedical care. Until now, the effects of a self-management intervention (SMI) addressing psychological and social issues for these patients and their partners have not been studied.

Objective: To examine the effects of a SMI i.e. the Patient and Partner Education Programme for Pituitary disease (PPEP-Pituitary).

Design and subjects: A multicentre randomized controlled trial included 174 patients with pituitary disease and 63 partners allocated to either PPEP-Pituitary or a control group. PPEP-Pituitary included eight weekly sessions (90 minutes). Self-efficacy, bother and needs for support, illness perceptions, coping, and QoL were assessed before the intervention (T0), directly after (T1), and after six months (T2). Mood was assessed before and after each session.

Results: Patients in PPEP-Pituitary reported improved mood after each session (except for session 1). In partners, mood only improved after the last three sessions. Patients reported higher self-efficacy at T1 (P=.016) which persisted up to T2 (P=.033), and less bother by mood problems directly after PPEP-Pituitary (P=.01), but more bother after six months (P=.001), although this increase was not different from baseline (P=.346). Partners in PPEP-Pituitary reported more vitality (P=.008) which persisted up to T2 (P=.034). At T2, partners also reported less anxiety and depressive symptoms (P≤.014).

Conclusion: This first study evaluating the effects of a SMI targeting psychosocial issues in patients with pituitary disease and their partners demonstrated promising positive results. Future research should focus on the refinement and implementation of this SMI into clinical practice.

INTRODUCTION

Patients with long-term biochemical remission of pituitary disease report impairments in Quality of Life (QoL) (1). Until now, little attention has been paid to interventions aiming at improving psychosocial aspects of QoL (2). The need for a psychosocial intervention in patients with pituitary disease was supported by results of recent focus group conversations reporting unmet needs regarding psychosocial care. Other reported issues in these focus groups were fatigue, increased sensitivity to stress, anxiety, depressive symptoms, difficulties communicating about the disease, and a reduced social network (3). In addition, a focus group study in partners of patients with pituitary disease reported that partners sometimes became annoyed by the tiredness and mood swings of their ill partner. Some partners felt they had to take on extra responsibilities at home (e.g. taking care of the children). They were aware of the negative consequences of the disease on their family, but they felt unable to cope emotionally or physically (4).

For patients with other chronic somatic diseases, psychosocial interventions, i.e. self-management interventions (SMIs), have been developed aiming to improve well-being of patients (5). Self-management is defined by Barlow et al. as "the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and life style changes inherent to living with a chronic condition. Efficacious self-management encompasses the ability to monitor one's condition and to affect the cognitive, behavioural and emotional responses necessary to maintain a satisfactory QoL" (6). SMIs in several chronic conditions (e.g. asthma, diabetes and arthritis) have demonstrated a positive effect on well-being of patients (6). Martire et al. (2010) demonstrated that couple-oriented interventions were more efficacious than psychosocial interventions that only included the patient or usual care (7). Although self-management interventions for any chronic disease may be based on general theoretical constructs, the composition and focus of the SMI also depends on the type of disease and self-management aims, e.g. focus on the prevention of exacerbations in asthma, or focus on lifestyle habits in diabetes (8).

There are only a few studies evaluating the effect of a SMI in patients with neuroendocrine disease. Martinez-Momblan et al. evaluated the effects of a 9-month educational nursing programme (5 visits) for patients with Cushing's syndrome in a randomized controlled trial (n=61). This educational programme included knowledge on Cushing's syndrome, comorbidities, treatment, general management, and autonomy in healthy lifestyles. Patients who followed this educational programme reported better disease-specific QoL, reduced pain, improved physical activity and a healthier lifestyle, compared to controls (9). Furthermore, Haugland et al. evaluated a 26-week educational programme in patients undergoing medical treatment for a neuroendocrine tumor in the gastrointestinal tract (n=37), and demonstrated improvement in physical components of QoL, reduced stress, and increased self-efficacy (10). These available SMI's focus primarily on education about Cushing's disease and its treatment and management (9) or education in patients with a neuroendocrine tumor in the gastro-

intestinal tract (10). Currently, a SMI for patients with pituitary disease and their partners addressing the psychosocial consequences and management of these consequences, of the disease is lacking.

Considering the patient and partner reported need for psychosocial care in pituitary disease, and the current lack of a SMI addressing psychological and social issues in these patients and their partners, the aim of the present study was to evaluate the effects of such a SMI in a randomized controlled trial in a large cohort of patients with pituitary disease and their partners.

PARTICIPANTS AND METHODS

Design

This multicentre two-arm randomized controlled trial was initiated by researchers at the department of Medicine of the Leiden University Medical Centre (LUMC). Patients were randomized for the SMI or the control group; 1:1 randomization was performed by the first author (CDA). Partners of patients who agreed to participate (n=63) were allocated to the same condition as their ill partner.

For ethical reasons, patients and partners who were randomized to the control group were also offered the SMI after the last measurement. The medical ethical committee of the LUMC approved the study, and written informed consent was obtained from all participants.

Participants (Figure 1)

The recruitment was coordinated by the out-patient departments of Medicine of the LUMC and the Radboud University Medical Centre (Radboudumc). Exclusion criteria were: <18 or >75 years of age; since older patients might have more comorbidity, current psychological treatment, current intensive medical treatment (e.g. radiotherapy, recovery from surgery) and psychiatric illness. A total number of 931 patients (and their partner when applicable) were informed about the study and were invited to participate (i.e. 462 from the LUMC; 469 from the Radboudumc). Reasons for not participating in the study were not speaking Dutch, not feeling comfortable talking in a group, too time consuming, burden too large (physically and/or mentally), not able to come due to other obligations (e.g. work, staying abroad, pregnancy, surgery), long travel distance, not perceiving problems, and no need for support (anymore), because patients already receive psychological counseling or previously received it, or learned to cope with their illness by themselves. One-hundred-and-eight patients (LUMC) and 80 patients (Radboudumc) agreed to participate. From the initial 188 incorporated patients, fourteen patients (7%) did not fill out the questionnaires. Therefore, a total number of 174 patients were included.

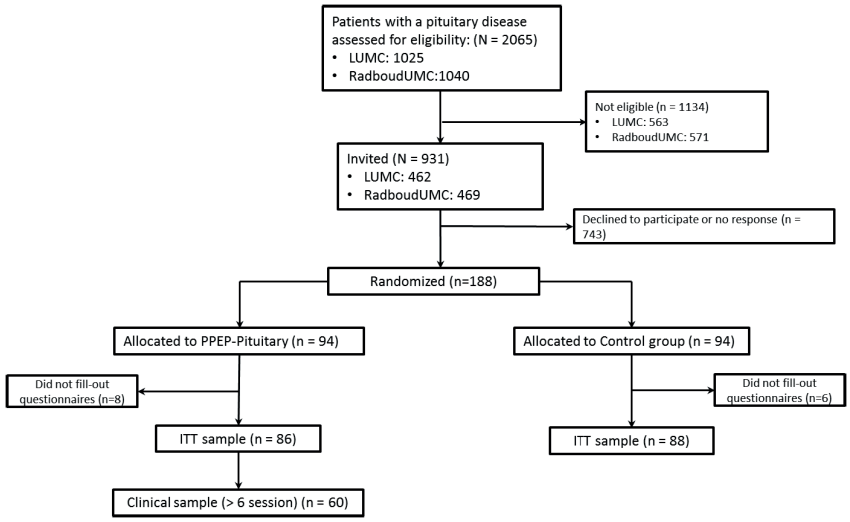

Figure 1. Flow-chart patients.

Development of the SMI

The SMI was based on the standardized Patient (and Partner) Education Programme initially developed for Parkinson's disease (PEPP), and evaluated in seven European countries (11;12) including the Netherlands (13-15), and is currently operational in patient care. The programme was then adapted for Huntington's disease (PEP-HD) (16) and was further developed and clinically tested in patients with chronic disease with psychiatric co-morbidity (17). Since the self-management techniques seemed to be generally applicable, the programme has recently been developed for patients with chronic disease in general (PPEP4ALL) (18). PPEP4ALL addresses psychological and social issues related to all chronic disease and uses techniques from cognitive behavioural therapy such as cognitive restructuring, systematic relaxation training, situational behavioural analyses, and training in social skills.

In order to assess whether PEPP was also suitable for patients with pituitary disease, focus group conversations in patients with pituitary disease were performed (3). The focus group guided us in laying the priorities and preferred options (e.g. fatigue, cognitive complaints, and problems with sexuality) within the PPEP4ALL. Based on these results we hypothesized PEPP/PPEP4ALL (Figure 2) would also be of relevance for patients with pituitary disease and their partners (when applicable). Then, we pilot tested it in 28 patients and 6 partners. Patients and partners reacted positively to the programme. Therefore, we decided to evaluate PPEP4ALL with the preferred options fatigue, cognitive complaints, and problems with sexuality. It was not necessary to drop any of the other components of PPEP4ALL and considering the patient group we named it the 'Patient and Partner Education Programme for Pituitary disease (PPEP-Pituitary)'.

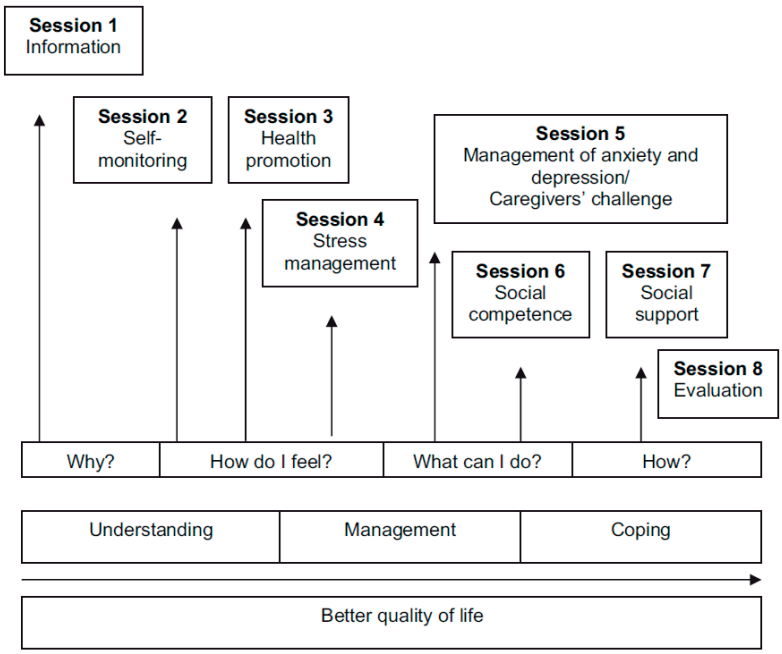

Figure 2. The themes and aims of the PPEP-Pituitary.
Figure derived from from A'Campo et al. (2010) (13).

PPEP-Pituitary

PPEP-Pituitary includes self-management components of potential relevance for pituitary disease, i.e. fatigue management, stress management, dealing with anxiety and depression, and communication training (Supplement 1). The programme consisted of eight weekly sessions of 90 minutes moderated by psychologists and medical social workers. Patients and partners participated separately and from their own perspective, in groups of 5-7 participants at the LUMC or at the Radboudumc. The same one or two trainers guided each group for 8 weeks (CDA, SM, RM, NF, MP-D, RG, JL, MS, MV). All trainers were trained in/experienced with the PPEP/PPEP4ALL, and followed a one-day training to get familiar with the disease-specific focus on pituitary disease.

Procedure

All included participants were asked to fill-out questionnaires prior to the programme (T0). Next, participants in PPEP-Pituitary followed the 8-week SMI, while the participants in the control group were invited for a single (optional) information meeting in week 4 or 5. For the formation of the patient groups, groups were stratified by disease in 3 groups i.e. 1) Cushing's disease (CD), 2) acromegaly or 3) prolactinoma/non-functioning pituitary adenoma (NFA)/ FSH-adenoma/craniopharyngeoma/hypopituitarism due to other causes. Partners in PPEP-

Pituitary were not stratified by pituitary disease of their partner. Participants were asked to fill-out the questionnaires again after the 8-week intervention (T1) and 6 months later (T2). Demographic characteristics (i.e. age, gender, marital status, education) and medication use were assessed by a self-report. Clinical characteristics of patients (e.g. type of pituitary disease, duration of follow-up) were derived from medical records.

Measures

For an overview of the used measures see Table 1.

Based on the preference of participants, questionnaires were sent by email (online survey) or by regular mail, to increase the response rate. Hundred-nine patients and 53 partners completed the questionnaires online, and 65 patients and 10 partners by postal survey. Previous research demonstrated that paper-and-pencil and online surveys do not lead to different results (19). Partners completed the same questionnaires except the LBNQ-Pituitary, the EQ-5D, the IPA, and the disease-specific QoL questionnaires (i.e. AcroQoL, CushingQoL). In addition, patients and partners in the PPEP-Pituitary group were asked to fill-out an evaluation form about PPEP-Pituitary (Supplement 2).

Statistical analyses

Data were analyzed using PASW Statistics version 20.0.0 (SPSS Inc., Chicago, IL). To check the normality of data, the Kolmogorov-Smirnov test was used. Demographic characteristics and the baseline scores (Supplement 3) were compared using independent sample t-test and Chi-square test when data were normally distributed and by using Mann-Whitney U test and Fisher's exact when data were not normally distributed. To compare pre- and post-session mood ratings paired sample t-tests were used. A linear mixed model with random participant effect, and fixed time and group effects, as well as group by time interactions measured the effects of the programme. The linear mixed model enables accommodating missing data points (20), and corrects for potential baseline differences. The effects of the programme were evaluated following intention to treat (ITT) principles, including all participants. Although ITT analysis is the golden standard for analyzing an RCT, it is also considered conservative (21) since not all participants in PPEP-Pituitary attended all sessions. Therefore, the post-hoc analyses comprised the clinical sample analyses including only the patients that attended at least six sessions, since this is the minimum amount of sessions to consider that someone completed PPEP-Pituitary, and since this situation will be more similar to the clinical situation. This analysis was performed using the same linear mixed model. The data from the evaluation were analyzed descriptively. Due to the explorative nature of this study, the level of significance was set at $P<0.05$. However, to take into account the effect of multiple testing, a Bonferroni correction was applied and a level of significance of $P<.005$ was also used.

Table 1. Measures

Questionnaire	Outcome	Subscales	Number of items	Range	Measurement time	Participants
Visual analogue scale-Mood (VAS-mood)	Mood	1	1	0-100, 0=extremely bad mood to 100=extremely good mood	Before and after each session	Patients & partners in PPEP-Pituitary
General Self-Efficacy Scale (GSE) (29, 30)	Self-efficacy	1	10	10-40, ↑scores indicate ↑self-efficacy	T0, T1, T2	Patients & partners in PPEP-Pituitary and control group
Leiden Bother and Needs Questionnaire for pituitary diseases (LBNQ-Pituitary) (31)	Bother and need for support	5: Mood, Negative illness perceptions, Issues in sexual functioning, Physical and cognitive complaints, Issues in social functioning	26	0-100, ↑scores indicate ↑bother and need for support	T0, T1, T2	Patients & partners in PPEP-Pituitary and control group
Brief Illness Perception Questionnaire (B-IPQ) (32)	Illness perceptions	8: Consequences, Personal control, Timeline, Treatment control, Identity, Concern, Coherence, Emotional response	8	0-10, 0=not at all to 10=very much	T0, T1, T2	Patients & partners in PPEP-Pituitary and control group
the Utrecht Coping List (UCL) (33)	Coping strategies	7: Active coping, Seeking distraction, Avoiding, Seeking social support, Passive coping, Expressing emotions, Fostering reassuring thoughts	47	Active coping (7-28) Seeking distraction (8-32), Avoiding (8-32), Seeking social support (6-24), Passive coping (7-28), Expressing emotions (3-12), Fostering reassuring thoughts (5-20). ↑scores indicate ↑more frequent performance of that coping	T0, T1, T2	Patients & partners in PPEP-Pituitary and control group
Impact on Participation and Autonomy (IPA) (34)	Participation and autonomy	5: family role, autonomy outdoors, autonomy indoors, social life and relationships, work and education	32	0-4, ↓scores indicate ↑participation and autonomy	T0, T1, T2	Patients & partners in PPEP-Pituitary and control group
EuroQoL-5D (EQ-5D)	(35)QoL	5: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression	5	1-3, ↑scores indicate ↓QoL	T0, T1, T2	Patients & partners in PPEP-Pituitary and control group
Short Form 36 (SF-36) (36, 37)	QoL	9: physical functioning, social functioning, role limitation (physical), role limitation (emotional), mental health, vitality, pain, general health perception, general perception of change in health	36	0-100, ↑scores indicate ↑QoL	T0, T1, T2	Patients & partners in PPEP-Pituitary and control group

Table 1. Measures (continued)

Questionnaire	Outcome	Subscales	Number of items	Range	Measurement time	Participants
Multidimensional Fatigue Inventory (MFI-20) (38)	Fatigue	5: General fatigue, Physical fatigue, Reduced activity, Reduced motivation, Mental fatigue	20	0-20, ↑scores indicate ↑fatigue	T0, T1, T2	Patients & partners in PPEP-Pituitary and control group
Hospital Anxiety and Depression Scale (HADS) (39, 40)	Anxiety and depression	2: anxiety, depressive symptoms	14	0-21, ↑scores indicate ↑anxiety/ depressive symptoms	T0, T1, T2	Patients & partners in PPEP-Pituitary and control group
AcroQoL (41-43)	Disease-specific QoL	3:physical, psychological-appearance, psychological-personal relations	22	0-100, ↓scores indicate ↓QoL	T0, T1, T2	Patients with acromegaly in PPEP-Pituitary and control group
CushingQoL (44-46)	Disease-specific QoL	2: Psychosocial issues, physical problems	12	0-100, ↓scores indicate ↓QoL	T0, T1, T2	Patients with CD in PPEP-Pituitary and control group

RESULTS

Baseline characteristics (Table 2)

Of the 188 patients incorporated, 94 patients were allocated to PPEP-Pituitary and 94 patients to the control group. Fourteen patients (8 in PPEP-Pituitary and 6 in the control group) did not complete any of the questionnaires and were not included in the ITT analysis. Therefore, a final number of 174 patients were included in the ITT analysis (PPEP-Pituitary: n=86 and control group: n= 88). Seventy percent of the patients (n=60) in PPEP-Pituitary attended at least 6 sessions i.e. the clinical sample.

From this clinical sample, 12 patients (20%) attended 6 sessions, 24 patients (40%) attended 7 sessions, and another 24 patients (40%) attended all 8 sessions.

From the patients in the control group, 42 patients (48%) attended the optional information meeting. Furthermore, 70% of the patients were married or in a relationship (n=122), and 63 partners (52%) were willing to participate. Twenty-five partners were in the PPEP-Pituitary group and 38 partners in the control group. From the partners in PPEP-Pituitary, 52% (n=13) attended at least 6 sessions (i.e. the clinical sample). From the partners in the control group, 16 (42%) attended the optional information meeting.

Mood changes after each PPEP-Pituitary session (Table 3)

Patient reported mood improved significantly after each session (all $P<.001$), except for session 1. Partners' mood improved only after sessions 6, 7, and 8 (all $P\leq.030$).

Effects of intervention: Intention to treat analysis (Table 4)

Self-efficacy

For patients a significant interaction was found for self-efficacy (GSE) (P=.020), with PPEP-Pituitary reporting more self-efficacy compared to controls (difference 1.35, P=.016) (T1 vs. T0), which persisted up to the 6 month follow-up (difference 1.74, P=.033) (T2 vs T0). No significant difference in self-efficacy was observed in partners.

Bother and Needs for support

An interaction was found for being bothered by mood problems (LBNQ-Pituitary) (P=.002), with PPEP-Pituitary, reporting to be less bothered by mood problems compared to controls (difference -6.27, P=.010) (T1 vs. T0). At T2 relative to T1, PPEP-Pituitary reported more bother by mood problems compared to controls (difference 8.71, P=.001), but this increase at T2 was not significantly different from baseline (difference 2.44, P=.346). Furthermore, an interaction was observed on the Total score of the Bothered by items of the LBNQ-Pituitary (P=.028), with PPEP-Pituitary reporting more overall bother (total score) at T2 relative to T1 compared to controls (difference 4.58, P=.008), but this increase at T2 was also not significantly different from baseline (difference 2.20, P=.219).

Table 2. Demographic variables of patients and partners

	Patients (n = 174)			Partners (n = 63)		
	PPEP-Pituitary group (n=86)	**Control group (n=88)**	**P value**	**PPEP-Pituitary group (n=25)**	**Control group (n=38)**	**P value**
Gender (M/F)	33/53	31/57	.667	17/8	18/20	.107
Age (years)	52.7 (11.9)	53.4 (12.7)	.600	55.7 (10.6)	58.9 (9.9)	.298
Condition-condition of ill partner			.866			.835
Cushing's disease	21 (24%)	19 (22%)		7 (28%)	6 (16%)	
Acromegaly	12 (14%)	10 (11%)		5 (20%)	7 (18%)	
Prolactinoma	18 (21%)	20 (23%)		3 (12%)	9 (24%)	
NFA	27 (31%)	30 (34%)		8 (32%)	13 (34%)	
FSH-adenoma	0 (0%)	1 (1%)		0 (0%)	0 (0%)	
Craniopharyngeoma	5 (6%)	3 (3%)		2 (8%)	0 (0%)	
*Hypopituitarism due to other causes**	3 (4%)	5 (6%)		0 (0%)	1 (3%)	
Education, n (%)			.219			.238
Low	20 (23%)	27 (31%)		4 (16%)	13 (34%)	
Medium	23 (27%)	29 (33%)		11 (44%)	11 (29%)	
High	42 (49%)	32 (36%)		10 (40%)	14 (37%)	
Unknown	1 (1%)	0 (0%)		0 (0%)	0 (0%)	
Marital status, n (%)			.027			NA
Single	16 (19%)	11 (13%)		0 (0%)	0 (0%)	
Relationship/marriage	55 (64%)	67 (76%)		25 (100%)	38 (100%)	
Divorced	8 (9%)	9 (10%)		0 (0%)	0 (0%)	
Widow	7 (8%)	0 (0%)		0 (0%)	0 (0%)	
Unkown	0 (0%)	1 (1%)		0 (0%)	0 (0%)	
Pituitary surgery, n (%)	60 (70%)	63 (72%)	.792	NA	NA	NA
Radiotherapy, n (%)	19 (22%)	21 (24%)	.781	NA	NA	NA
Duration since diagnosis (yrs)	11.7 (10.8)	13.0 (13.5)	.884	NA	NA	NA
Hypopituitarism, n (%)						
ACTH	40 (47%)	50 (57%)	.174	NA	NA	NA
TSH	42 (49%)	46 (52%)	.650	NA	NA	NA
LH/FSH	40 (47%)	41 (47%)	.992	NA	NA	NA
GH	36 (42%)	40 (46%)	.633	NA	NA	NA
ADH	6 (7%)	8 (9%)	.608	NA	NA	NA

*traumatic brain injury, Sheehan, pituitary ischaemia, e causa ignota (eci). NA: not applicable.

Table 3. Pre- and post-session mood-VAS ratings (range 0-100) of patients and partners

	Patients (n = 54-70)			**Partners (n = 10-15)**		
Session	**Before session**	**After session**	**P value**	**Before session**	**After session**	**P value**
1	69.91 (13.14)	70.94 (12.09)	.384	71.15 (10.24)	71.92 (12.17)	.776
2	68.03 (14.83)	74.32 (12.27)	**<.001***	72.00 (9.02)	73.13 (10.46)	.687
3	65.27 (14.48)	73.11 (12.41)	**<.001***	68.75 (14.32)	74.83 (9.11)	.090
4	68.96 (12.93)	75.39 (10.32)	**<.001***	70.58 (8.37)	73.42 (7.83)	.055
5	68.77 (10.55)	73.55 (11.94)	**<.001***	73.60 (8.51)	73.40 (7.90)	.920
6	67.96 (12.81)	73.18 (11.22)	**<.001***	73.00 (6.95)	77.17 (6.46)	**.005***
7	70.76 (10.02)	75.25 (9.43)	**<.001***	75.08 (7.32)	78.15 (7.03)	**.025***
8	70.65 (10.48)	77.93 (9.33)	**<.001***	73.08 (6.09)	77.54 (7.66)	**.030***

All data are mean (sd) * P<0.05.

Illness perceptions

No significant differences in illness perceptions (B-IPQ) were observed for patients over time.

For partners an interaction was found for perceived treatment control (P=.025), with PPEP-Pituitary perceiving more treatment control compared to controls (difference 3.12, P=.008) (T2 vs. T1), but this increase at T2 was not significant from baseline (difference 1.43, P=.230)

Coping

No significant differences in coping styles (UCL) were found for patients and partners over time.

P*articipation and autonomy*

No significant differences in participation and autonomy (IPA) were found for patients over time.

Quality of life

For patients no significant differences were found for QoL (i.e. EQ-5D, SF-36, MFI-20, HADS, CushingQoL, AcroQoL).

For partners an interaction was found for vitality (SF-36) (P=.026), with PPEP-Pituitary reporting more vitality compared to controls (difference 14.03, P=.008) (T1 vs. T0), which persisted up to the 6 month follow-up (difference 15.45, P=.034) (T2 vs. T0). Furthermore, an interaction was found for anxiety (HADS) (P=.035), with PPEP-Pituitary reporting less anxiety at T2 relative to T0 (difference -2.65, P=.014). In addition, an interaction was found for depressive symptoms (HADS) (P=.012), with PPEP-Pituitary reported less depressive symptoms at T2 relative to T0 (difference -3.47, P=.003), as well as at T2 relative to T1 (difference -2.60, P=.012). Finally, an interaction was found for the HADS total score (P=.005), with PPEP-Pituitary re-

porting a lower total HADS score at T2 relative to T0 (difference -6.51, P=.002), as well as at T2 relative to T1 (difference -4.54, P=.034) compared to controls.

Table 4. Changes in the outcome measures in patients and partners (ITT sample)

	Patients (n=174)				Partners (n=63)			
	ΔPPEP-Control T0-T1	ΔPPEP-Control T1-T2	ΔPPEP-Control T0-T2	P value groupxtime	ΔPPEP-Control T0-T1	ΔPPEP-Control T1-T2	ΔPPEP-Control T0-T2	P value groupxtime
LBNQ-Pituitary								
Bother by								
Mood problems	-6.27*	8.71#	2.44	.002#	NA	NA	NA	NA
Negative illness perceptions	-2.14	4.03	1.89	.176	NA	NA	NA	NA
Issues in sexual functioning	2.92	2.02	4.94	.272	NA	NA	NA	NA
Physical & cognitive complaints	-0.77	4.66	3.89	.127	NA	NA	NA	NA
Issues in social functioning	-3.06	1.54	-1.52	.347	NA	NA	NA	NA
Total score	-2.37	4.58*	2.20	.028*	NA	NA	NA	NA
Need for support								
Mood problems	-4.69	8.26	3.57	.073	NA	NA	NA	NA
Negative illness perceptions	-1.92	6.33	4.41	.131	NA	NA	NA	NA
Issues in sexual functioning	4.09	2.03	6.12	.309	NA	NA	NA	NA
Physical & cognitive complaints	0.79	5.85	6.63	.077	NA	NA	NA	NA
Issues in social functioning	-4.38	2.75	-1.64	.199	NA	NA	NA	NA
Total score	-1.65	5.17	3.53	.078	NA	NA	NA	NA
EQ-5D								
Mobility	-0.07	0.04	-0.03	.509	NA	NA	NA	NA
Selfcare	0.01	0.01	0.02	.904	NA	NA	NA	NA
Daily activity	-0.15	0.05	-0.10	.167	NA	NA	NA	NA
Pain	-0.03	-0.04	-0.06	.781	NA	NA	NA	NA
Mood	-0.06	-0.05	-0.10	.408	NA	NA	NA	NA
VAS	-3.63	0.84	-2.79	.352	NA	NA	NA	NA
SF-36								
Physical functioning	3.45	-4.82	-1.37	.211	1.95	7.66	9.62	.302
Social functioning	2.08	-1.92	0.17	.722	3.04	14.71	17.75	.084
Role limitations-Physical	2.39	-12.03	-9.64	.203	-6.87	29.52	22.65	.111
Role limitations-Emotional	-3.31	3.19	-0.12	.831	-15.99	30.92	14.93	.156
Mental Health	1.63	-2.18	-0.55	.480	-6.26	11.61	5.35	.330
Vitality	3.14	-3.43	-0.29	.284	14.03*	1.42	15.45*	.026*
Pain	-2.62	-0.79	-3.40	.505	-4.42	9.57	5.15	.281
General Health	-0.62	3.77	3.14	.179	2.82	-2.66	0.17	.729
Health change	.03	-7.79	-7.50	.234	12.72	8.74	21.46	.083
MFI-20								
General fatigue	-0.37	0.40	0.03	.441	1.18	-0.58	0.61	.215
Physical fatigue	0.20	-0.42	-0.22	.389	-0.13	-0.10	-0.23	.932
Reduced activity	-0.20	0.27	0.07	.731	0.44	-0.70	-0.26	.700
Reduced motivation	0.07	0.02	0.10	.961	-0.40	-0.48	-0.88	.373
Mental fatigue	0.37	1.44	1.82	.107	-0.16	-0.88	-1.04	.152

Table 4. Changes in the outcome measures in patients and partners (ITT sample) (continued)

	Patients (n=174)				Partners (n=63)			
	ΔPPEP-Control T0-T1	ΔPPEP-Control T1-T2	ΔPPEP-Control T0-T2	P value groupxtime	ΔPPEP-Control T0-T1	ΔPPEP-Control T1-T2	ΔPPEP-Control T0-T2	P value groupxtime
HADS								
Anxiety	-0.09	0.07	-0.02	.976	-0.91	-1.74	-2.65*	.035*
Depression	-0.36	0.99	0.63	.056	-0.87	-2.60*	-3.47#	.012*
Total score	-0.50	1.20	0.71	.221	-1.97	-4.54*	-6.51#	.005#
B-IPQ								
Consequences	0.03	0.50	0.54	.221	0.64	-0.23	0.41	.770
Timeline	-0.28	0.27	-0.01	.662	-0.42	0.38	-0.04	.712
Personal control	-0.46	-0.22	-0.68	.430	1.07	0.45	1.53	.504
Treatment control	-0.11	0.43	0.32	.547	-1.69	3.12*	1.43	.025*
Identity	-0.25	0.07	-0.18	.773	-0.24	0.79	0.55	.589
Coherence	-1.12	0.47	-0.65	.491	-1.13	0.29	-0.83	.142
Emotional representations	0.68	0.05	0.73	.133	0.29	0.57	0.86	.737
Concerns	-0.51	0.77	0.26	.108	-0.63	1.30	0.67	.359
UCL								
Active coping	-0.26	-0.27	-0.53	.808	1.25	0.84	2.09	.628
Seeking distraction	0.99	-0.16	0.83	.348	-0.88	2.48	1.60	.191
Avoiding	0.31	0.27	0.58	.711	0.35	0.36	0.71	.834
Seeking social support	-0.48	0.21	-0.26	.544	0.71	-1.63	-0.92	.501
Passive coping	0.41	0.64	1.05	.281	-0.96	0.20	-0.76	.503
Expression of emotions	0.07	-0.07	0.00	.944	-0.35	0.38	0.03	.771
Fostering reassuring thoughts	-0.16	-0.04	-0.20	.907	-1.31	1.63	0.33	.111
GSE								
Total score	1.35*	0.39	1.74*	.020*	0.45	-0.77	-0.32	.830
IPA								
Autonomy indoors	-0.01	.12	0.11	.247	NA	NA	NA	NA
Familiy role	-0.00	-0.03	-0.03	.956	NA	NA	NA	NA
Autonomy outdoors	-0.08	0.01	-0.07	.657	NA	NA	NA	NA
Social life and relationships	0.06	-0.34	0.02	.694	NA	NA	NA	NA
Work and education	-0.07	0.26	0.19	.869	NA	NA	NA	NA
CushingQoL†								
Psychosocial issues	4.16	-4.36	-0.20	.337	NA	NA	NA	NA
Physical problems	3.68	-1.06	2.63	.666	NA	NA	NA	NA
Total score	3.83	-4.07	-0.24	.304	NA	NA	NA	NA
AcroQoL‡								
Physical score	3.32	-15.64	-12.31	.101	NA	NA	NA	NA
Psychological-appearance	-6.72	-2.05	-8.77	.504	NA	NA	NA	NA
Psychological-personal relations	5.65	-18.17	-12.52	.124	NA	NA	NA	NA
Total score	1.25	-12.16	-10.91	.149	NA	NA	NA	NA

* P<.05, # P<.005. †Only patients with Cushing's disease; ‡Only patients with acromegaly. LBNQ-Pituitary, Leiden Bother and Needs Questionnaire for pituitary diseases; EQ-5D, EuroQoL-5D; SF-36, Short Form 36; MFI-20, Multidimensional Fatigue Inventory; HADS, Hospital Anxiety and Depression Scale; B-IPQ, Brief Illness Perception Questionnaire; UCL, Utrecht Coping List; GSE, General Self-Efficacy Scale; IPA, Impact on Participation and Autonomy questionnaire. P value group x time: significance of the interaction i.e. PPEP-Pituitary vs. control group x time point (i.e. baseline (T0), directly after PPEP-Pituitary (T1), 6 months follow-up (T2)).

Post-hoc analysis: Clinical sample

All findings from the ITT analyses were also observed in the clinical sample analysis (Supplement 4). However, some new findings were observed. Patients in PPEP-Pituitary reported a higher need for support for coping with negative illness perceptions (LBNQ-Pituitary) than controls (difference 7.88, P=.018) at T2 relative to T1, but this increase at T2 was not significantly different from baseline (difference 3.14, P=.422). Furthermore, PPEP-Pituitary reported a higher need for support for physical and cognitive problems (LBNQ-Pituitary) at T2 relative to T1 (difference 7.01, P=.023) which was also significantly different from baseline (difference 7.43, P=.036). PPEP-Pituitary reported more depressive symptoms (HADS) (difference 1.17, P=.008) at T2 relative to T1, but this increase at T2 was not significantly different from baseline (difference 0.67, P=.191). Partners in PPEP-Pituitary reported better social functioning (SF-36) at T2 relative to T1 (difference 19.70, P=.023) compared to controls, which was also significantly different from baseline (difference 22.30, P=.012).

Patient and partner evaluation

Of the patients who followed at least 6 sessions i.e. the clinical sample (n=60), 55 patients filled-out the evaluation form (92%). Ninety-five percent of the patients agreed that the exchange of experiences within the group was helpful, and over half of the patients (53%) reported a better understanding of the psychological effects of their disease. Two thirds of the patients (67%) reported their expectations were fulfilled, and 84% would recommend the programme to other patients. All partners who followed at least 6 sessions (n=13), filled-out the evaluation form. All partners agreed that the exchange of experiences was helpful; two thirds of the partners (62%) reported a better understanding of the psychological effects of the disease. In 54% of the partners their expectations were fulfilled and 77% would recommend the programme to other partners.

DISCUSSION

PPEP-Pituitary resulted in enhanced self-efficacy in patients which persisted after the 6 month follow-up. Perceived bother by mood problems decreased directly after PPEP-Pituitary, but returned to baseline level after 6 month follow-up. Partners reported more vitality immediately after PPEP-Pituitary, which was still present after 6 months. Partners also reported less anxiety and depressive symptoms after 6 months. Furthermore, mood improved after each session (except for session 1) in patients and after the last three sessions in partners.

Similar to the results of the SMI described by Haugland et al. (10), PPEP-Pituitary enhanced self-efficacy in patients. The term self-efficacy is described in the 'Social Cognitive Theory' of Bandura (22) and defined as the person's beliefs in his or her own capabilities to perform a certain action, in a certain environment. Following this model, behaviour is directly influenced by goals and self-efficacy expectations. In line with this model, several studies demonstrated

that self-efficacy influences self-management behaviour (23;24), as well as SMIs improving self-efficacy in patients with chronic disease (25;26). For instance, Steed et al. evaluated a SMI which was based on the Social Cognitive Theory and demonstrated a positive effect on diabetes self-management behaviour, i.e. diabetes-specific-diet, exercise and blood glucose monitoring (27). Following Bandura, self-efficacy can be increased and behaviour change enhanced by four components: 1) mastery, which refers to the direct experience of success in performing a certain behaviour; 2) vicarious experience which refers to modelling gained by successful behaviour of a person with whom one identifies (e.g. person with the same illness); 3) social persuasion e.g. encouragement from health professionals or members of the self-management group; and 4) reducing feelings of stress and altering negative emotional tendencies, since this may lead to reducing misinterpretations of physical symptoms or one's physical state (28). All four components were used in PPEP-Pituitary.

The results of the ITT analysis were further confirmed by the analyses including only participants that followed at least six sessions (i.e. the clinical sample). In the clinical sample analysis as well as in the ITT analysis we observed that depressive symptoms and bother by mood problems increased during 6 month follow-up after PPEP-Pituitary, although not different from baseline levels. Furthermore, the clinical sample analysis complemented the ITT results by observations that patients reported a higher need for support for coping with negative illness perceptions and physical and cognitive problems. This finding might be explained by the fact that patients in PPEP-Pituitary learned skills to concretize/verbalize their healthcare needs, but also suggests that it might be useful to implement one or two additional refreshing/booster sessions during follow-up e.g. after 6 months or even over 12 months. On the other hand, partners reported an increase in social functioning 6 months after PPEP-Pituitary. This seems to indicate that partners needed time to implement the newly learned skills in their daily lives. It could also be that aspects of QoL improved in partners as a result of the improvement in self-efficacy in their ill partners.

In the present study we did not observe any effects in patients on QoL, illness perceptions, coping, and autonomy and participation in different life domains. It should, however, be noted there was a relatively long duration since diagnosis (i.e. PPEP-Pituitary: 12 years, control group: 13 years). It is conceivable that during this long period of living with the disease, patients and partners adapted to the consequences of the disease and/or already had received appropriate support, which may have limited the beneficial effects of our programme in improving psychosocial aspects. It should also be realized that although some aspects did not change during the time of the study, it could be that due to the learned psychosocial skills, patients and partners became more resilient to develop psychosocial morbidity, and future research into this area is warranted.

Due to the explorative nature of the present study, a large number of outcome parameters was used which could have led to a higher chance of type I error. After the post-hoc Bonferroni correction, the effect on mood problems in patients and the effect on anxiety and

depressive symptoms could still be observed. Furthermore, the large number of outcome parameters could also have influenced the response rate of the participants, considering the duration of filling-out the questionnaires. In addition, it should be acknowledged that self-management is by definition largely implemented by the participants themselves with limited external supervision. For instance, it is not known how often participants practised the learned skills at home. This information could have provided additional insight into the effects of the program, and should therefore be taken into account in future research by for instance asking participants to keep up a diary. Another limitation related to research in SMIs is that they largely rely on self-report measures. The measures used in this study were all validated, but probably not equal to direct observation.

A strength of the present study is the inclusion of both patients and partners, and the relatively large sample size. In addition, the variability in included centres, as well as in trainers (n=9) (i.e. psychologist, medical social workers) increases the validity of the effect of PPEP-Pituitary. For future implementation of the programme in (other) medical centres, PPEP-Pituitary can be provided by psychologist and social workers, but also by other health care professionals such as endocrine nurses as long as they are trained in the principles of PPEP-Pituitary and have an appropriate level of knowledge about pituitary disease. Sixty-seven percent of the patient reported that their expectation about PPEP-Pituitary were met. From the notes written on the evaluation forms it became apparent that patients would have liked more (practical, medical) information about their disease (i.e. bodily changes due to disease, medication, side-effects). Therefore, we are considering the invitation of an endocrine nurse to the first session to provide (practical) information about the disease. For future implementation of PPEP-Pituitary, it is very difficult to form separate groups per disease (i.e. CD, acromegaly, NFA/PRL), considering the low incidence of pituitary adenomas. Therefore, we postulate that groups can be formed with patients with different pituitary diseases. This seems to be suitable considering the overlapping symptoms (i.e. hypopituitarism, fatigue), but on the other hand it can be imagined that for a patient it can be helpful to have at least one other person in the group with the same disease. Future implementation of PPEP-Pituitary groups of patients with different pituitary diseases can be formed, but with taking into account the distribution of diseases per group. Furthermore, a question that needs to be further clarified in future research is determining the best moment to offer PPEP-Pituitary during the disease process. We believe that directly after biomedical treatment is not the right moment, because patients need their time and energy to recover from treatment, but also because patients will not have a clear idea about the psychosocial consequences of the disease making it difficult to work on during PPEP-Pituitary. On the other hand, when the programme is offered years after biomedical treatment, patient may have learned to cope with the consequences and/or they had to search for psychological care by themselves. Therefore, we postulated that the ideal moment to offer the programme will be between 6-12 months after biochemical remission. It is speculated that offering the programme at that time might

lead to less healthcare consumption. Therefore, for future research it would be interesting to assess the effects of PPEP-Pituitary in a clinical setting that also includes patients that have recently obtained a stable medical situation.

In conclusion, this first study about the effects of PPEP-Pituitary in a large cohort of patients with on average a relatively long duration since diagnosis, demonstrated that PPEP-Pituitary enhances self-efficacy in patients, and their partners report better QoL in the long-term. We postulate that implementing PPEP-Pituitary in clinical care will (at least partly) meet the current unmet needs regarding psychosocial care in patients with pituitary disease and their partners. For the implementation of PPEP-Pituitary we are currently evaluating the approach to schedule one or two additional refreshing/booster sessions after 6 months or 12 months. Future research will need to focus on the implementation of this programme into clinical care trajectories.

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SUPPLEMENT 1.

Session	Structure	Main focus
1. Information	Introduction	• Acquaintance with each other • Overview of the program is provided • Participant expectations and needs are elucidated
	Active information	• The importance of taking an active and central role in the health care system
	Exercise	• How to ask questions to healthcare professionals
	Homework	• To draft questions for a visit to health care professionals
	Appetizer	Past experiences with keeping a diary/journal
2. Self-monitoring	Homework discussion	Homework discussion of session 1
	Active information	• To learn about self-monitoring techniques, such as a diary • Fatigue management by self-monitoring and behavioral adaptations
	Exercise	An exercise 'body-awareness' focused on breathing and muscular tension
	Homework	• Using a diary to record e.g. fluctuations in fatigue or mood • Performing the exercise 'body awareness'
	Appetizer	Bringing something pleasant to the next session (e.g. an object or experience)
3. Health promotion	Homework discussion	Homework discussion of session 2
	Active information	To improve well-being through pleasant activities
	Exercise	Exploring pleasant activities
	Homework	To plan and perform one or more pleasant activities in the upcoming week
	Appetizer	Observing your own behavior in stressful situations
4. Stress-management	Homework discussion	Homework discussion of session 3
	Active information	The role of unrealistic and unhelpful thoughts in stressful situations
	Exercise	Learning to use alternative ways of thinking; Performing relaxation exercises to deal with stress
	Homework	• Trying out alternative ways of thinking • Relaxation training
	Appetizer	Observing changes of mood and causes of worry
5. Management of anxiety & depression Challenges for partners	Homework discussion	Homework discussion of session 4
	Active information	• To learn about the difference between normal feelings of anxiety and sadness and when they turn into anxiety disorders or depression -partner/caregiver overload • To learn about the role of unrealistic, unhelpful cognitions Potential issues with a decreased libido and problems in sexual functioning are discussed
	Exercise	Positive thoughts and rewards; Maintaining health activities (patients/partners)
	Homework	• Positive thoughts and rewards (patients) • Thinking of a positive event (partners) • Maintaining health activities (patients/partners)
	Appetizer	Noticing situations in which you want to express your thoughts and feelings but do not have the confidence to do so

6.	Social competence	Homework discussion	Homework discussion of session 5
		Active information	Social skills to communicate are discussed
		Exercise	To learn about unhelpful and helpful thoughts in communication and ways of communication
		Homework	• Noticing situations in which helpful thoughts contributed to a lack of socially competent behavior • Telling someone that you have a pituitary disease
		Appetizer	To focus on the informal and formal support they currently have and what they would like to receive
7.	Social support	Homework discussion	Homework discussion of session 6
		Active information	To discuss the importance of social support and how to obtain social support
		Exercise	Role play/discussion
		Homework	Finding sources of support and asking for support
		Appetizer	Reflecting about the entire program
8.	Evaluation	Homework discussion	Homework discussion of session 7
		Active information	• The group goes through the previous sessions and the program is evaluated • Expectations and achievements are compared
		Exercise	Writing a postal card for each other and filling out the evaluation questionnaire

Adapted from A'Campo et al. (2010) (13). Topics are the same for patients and partner although they participate in separate groups. Only session 5 has a different topic for patients and partners, i.e., patients learn about the management of anxiety and depression, while partners learn about challenges for being a partner of a patient with pituitary disease.

SUPPLEMENT 2. EVALUATION QUESTIONNAIRE

Below are statements relevant to the education programme you have just completed. For each statement, please tick the box that best reflects your opinion.

		Disagree	Agree somewhat	Agree
1.	I have received helpful information about the pituitary disease and the possible psychosocial problems related to the pituitary disease.			
2.	The exchange of experiences and ideas within the group was helpful.			
3.	The information presented in the programme often confused me.			
4.	I would have liked even more information to be presented.			
5.	Too much theoretical information was given during the programme.			
6.	Much of the information was new to me.			
7.	My understanding of the pituitary disease and the problems associated with the pituitary disease has improved.			
8.	I believe that I can now deal better with the problems related to the pituitary disease.			
9.	Too little practical information was given during the programme.			
10.	I found some of the exercises too difficult.			
11.	My understanding of the psychological effects of the pituitary disease has improved.			
12.	In general, the programme fulfilled my expectations.			
13.	The programme was appropriate for me.			
14.	I would participate in another programme of a similar nature if available.			
15.	I would recommend this programme to other people.			

SUPPLEMENT 3. BASELINE SCORES

	Patients (n=174)		Partners (n=63)	
	PPEP-Pituitary group (n=86)	Control group (n=88)	PPEP-Pituitary group (n=25)	Control group (n=38)
LBNQ-Pituitary				
Bb-Mood problems	24.3 (22.5)	24.1 (21.8)	NA	NA
Bb-Negative illness perceptions	18.5 (21.8)	19.1 (17.8)	NA	NA
Bb-Issues in sexual functioning	18.4 (24.1)	22.5 (24.4)	NA	NA
Bb-Physical and Cognitive complaints	31.0 (25.9)	34.5 (21.9)	NA	NA
Bb-Issues in Social functioning	17.6 (22.8)	15.2 (18.4)	NA	NA
Bb-Total score	23.0 (19.7)	24.2 (17.3)	NA	NA
NfS-Mood problems	31.5 (27.8)	31.1 (27.1)	NA	NA
NfS-Negative illness perceptions	27.0 (27.5)	29.9 (26.1)	NA	NA
NfS-Issues in sexual functioning	21.5 (26.7)	26.4 (30.0)	NA	NA
NfS-Physical and Cognitive complaints	36.9 (29.5)	40.8 (28.8)	NA	NA
NfS-Issues in Social functioning	21.9 (26.6)	19.3 (22.3)	NA	NA
NfS-Total score	29.1 (23.3)	30.7 (23.3)	NA	NA
EQ-5D				
Mobility	1.4 (0.5)	1.4 (0.5)	1.1 (0.3)	1.2 (0.4)
Selfcare	1.1 (0.3)	1.1 (0.3)	1.0 (0.0)	1.0 (0.2)
Daily activity	1.5 (0.6)	1.5 (0.5)	1.1 (0.2)	1.3 (0.4)
Pain	1.6 (0.6)	1.7 (0.6)	1.5 (0.5)	1.6 (0.6)
Mood	1.4 (0.6)	1.4 (0.5)	1.1 (0.2)	1.5 (0.5)
VAS	68.4 (15.7)	64.4 (19.9)	77.4 (13.1)	77.0 (16.4)
SF-36				
Physical functioning	74.0 (26.3)	67.9 (25.1)	90.0 (16.3)	85.2 (19.9)
Social functioning	69.8 (26.3)	71.2 (23.2)	90.3 (20.4)	78.1 (25.4)
Role limitations-Physical	54.3 (43.9)	49.7 (43.9)	91.7 (25.7)	79.5 (36.0)
Role limitations-Emotional	71.5 (39.6)	71.8 (40.0)	90.7 (25.1)	75.0 (42.2)
Mental Health	65.6 (17.2)	68.8 (16.7)	80.9 (10.4)	72.1 (16.7)
Vitality	50.2 (22.0)	49.2 (21.2)	68.9 (19.0)	64.6 (19.9)
Pain	73.4 (26.7)	69.3(24.4)	90.6 (11.1)	78.9 (23.6)
General Health	50.0 (15.8)	51.4 (16.1)	**31.9 (13.3)**	**50.4 (19.4)**
Health change	54.0 (25.3)	49.7 (23.6)	50.0 (17.1)	55.2 (21.5)
MFI-20				
General fatigue	11.6 (2.3)	11.6 (1.6)	12.2 (1.5)	12.0 (1.2)
Physical fatigue	13.4 (1.5)	13.5 (2.1)	12.9 (1.5)	13.0 (1.3)
Reduced activity	12.3 (2.0)	12.2 (1.9)	13.1 (2.0)	13.9 (6.2)
Reduced motivation	11.5 (2.2)	12.0 (2.0)	12.2 (1.2)	12.4 (1.9)
Mental fatigue	11.1 (1.9)	11.3 (1.8)	11.6 (0.7)	11.4 (1.7)

	Patients (n=174)		Partners (n=63)	
	PPEP-Pituitary group (n=86)	**Control group (n=88)**	**PPEP-Pituitary group (n=25)**	**Control group (n=38)**
HADS				
Anxiety	5.8 (4.1)	5.9 (4.0)	4.0 (2.9)	6.3 (4.3)
Depression	4.6 (3.8)	5.3 (3.7)	3.3 (4.1)	4.9 (4.7)
Total score	10.4 (7.0)	11.3 (6.9)	7.3 (6.2)	11.2 (8.7)
IPQ-brief				
Consequences	5.6 (2.9)	6.0 (2.6)	4.2 (3.2)	5.2 (3.3)
Timeline	8.7 (2.7)	9.2 (2.1)	9.8 (.07)	9.3 (2.5)
Personal control	5.3 (3.0)	4.8 (3.0)	5.3 (3.8)	5.1 (3.4)
Treatment control	7.3 (2.7)	7.5 (2.4)	6.9 (2.9)	7.0 (2.9)
Identity	5.8 (2.8)	5.6 (2.6)	6.2 (2.9)	6.3 (2.9)
Coherence	6.8 (2.7)	6.5 (2.2)	8.3 (1.6)	7.5 (2.1)
Emotional representations	**4.2 (3.0)**	**5.4 (2.8)**	**2.5 (2.3)**	**4.7 (3.1)**
Concerns	4.4 (2.8)	4.7 (2.7)	5.1 (3.0)	5.9 (3.2)
UCL				
Active coping	18.6 (6.4)	17.5 (5.7)	20.0 (3.9)	19.0 (7.3)
Seeking distraction	17.2 (3.9)	17.5 (5.6)	15.5 (3.8)	15.8 (3.8)
Avoiding	16.1 (3.0)	17.6 (6.0)	15.3 (2.9)	15.0 (3.6)
Seeking social support	12.7 (4.0)	12.4 (3.8)	11.9 (2.1)	11.8 (3.8)
Passive coping	12.3 (3.2)	12.6 (6.6)	10.1 (2.7)	10.6 (3.0)
Expression of emotions	5.5 (1.5)	5.5 (1.7)	4.8 (1.4)	4.8 (1.1)
Fostering reassuring thoughts	12.4 (3.6)	12.5 (3.1)	11.6 (2.6)	10.8 (2.4)
GSE				
Total score	29.6 (4.8)	29.8 (5.1)	**33.2 (3.2)**	**30.4 (5.0)**
IPA				
Autonomy indoors	**0.5 (0.6)**	**0.6 (0.6)**	NA	NA
Familiy role	1.1 (1.0)	1.2 (0.9)	NA	NA
Autonomy outdoors	1.4 (1.1)	1.3 (0.8)	NA	NA
Social life and relationships	1.0 (0.7)	1.0 (0.7)	NA	NA
Work and education	2.3 (4.2)	3.0 (5.4)	NA	NA
CushingQoL#	37.6 (10.6)	36.4 (8.2)	NA	NA
Psychosocial issues	54.1 (25.7)	49.2 (19.9)	NA	NA
Physical problems	51.2 (22.6)	55.1 (19.0)	NA	NA
Total score	53.4 (22.0)	50.7 (17.5)	NA	NA
AcroQoL^				
Physical score	58.8 (16.5)	51.6 (15.6)	NA	NA
Psychological-appearance	52.9 (22.2)	42.0 (20.0)	NA	NA
Psychological-personal relations	73.1 (15.2)	76.0 (13.9)	NA	NA
Total score	61.5 (16.0)	58.4 (12.8)	NA	NA

Bold P< .05. Mann-Whitney U tests. #only assessed in patients with Cushing's disease; ^only assessed in patients with acromegaly. NA: not applicable.

SUPPLEMENT 4. POST-HOC ANALYSIS: CLINICAL SAMPLE

Self-efficacy

Similar to the results of the ITT analyses, a significant interaction was found for self-efficacy (GSE) (P=.013), with PPEP-Pituitary reporting more self-efficacy (difference 1.66, P=.007) compared to controls (T1 vs. T0), which persisted up to the 6 month follow-up (difference 1.77, P=.044) (T2 vs T0). No significant difference in self-efficacy was observed in partners.

Bother and Needs for Support

Similar to the results of the ITT analyses, an interaction was revealed on being bothered by mood problems (P=.006), with PPEP-Pituitary reporting to be less bothered by mood problems compared to controls (LBNQ-Pituitary) (difference -6.67, P=.011) at T1 relative to T0. At T2 relative to T1 PPEP-Pituitary reported more bother by mood problems compared to controls (difference 8.54, P=.003), but this increase was not significantly different from baseline (difference 1.87, P=.483). In addition, an interaction was found for the Total bother score (LBNQ-Pituitary) (P=.023), with PPEP-Pituitary reporting a higher Total bother score compared to controls (difference 5.11, P=.006) at T2 relative to T1, but this increase was also not significantly different from baseline (difference 2.44, P=.193). New findings raised in the clinical sample analyses were that there was a significant interaction for need for support for negative illness perceptions (LBNQ-Pituitary) (P=.048), with PPEP-Pituitary reporting a higher need for support than controls (difference 7.88, P=.018) at T2 relative to T1, but this increase was not significantly different from baseline (difference 3.14, P=.422). Furthermore, an interaction was found for need for support for physical and cognitive problems (LBNQ-Pituitary) (P=.046), with PPEP-Pituitary reporting a higher need for support compared to controls at T2 relative to T0 (difference 7.43, P=.036) and at T2 relative to T1 (difference 7.01, P=.023).

Illness perceptions

Similar to the results of the ITT analyses in patients, no significant differences in illness perceptions were observed (B-IPQ).

Similar to the observations of the ITT analyses in partners, an interaction was found for perceived treatment control (B-IPQ) (P=.045), with PPEP-Pituitary reporting more treatment control compared to controls at T2 relative to T1 (difference 3.24, P=.016), but this increase at T2 was not significantly different from baseline (difference 1.26, P=.360).

Coping

Similar to the observations of the ITT analyses, no significant differences in coping styles (UCL) were found for patients and partners.

Participation and autonomy

Similar to the observations of the ITT analyses, no significant differences in participation and autonomy (IPA) were found for patients.

Quality of life

In contrast to the ITT analyses in patients, a significant interaction was found for depressive symptoms (HADS) (P=.027), with PPEP-Pituitary reporting more depressive symptoms compared to controls at T2 relative to T1 (difference 1.17, P=.008), but this increase was not significantly different from baseline (difference 0.67, P=.191).

Similar to the results of the ITT analyses in partners, an interaction was found for vitality (SF-36) (P=.029), with PPEP-Pituitary reporting more vitality compared to controls (difference 15.70, P=.009) (T1 vs. T0), which persisted up to 6 month follow-up (difference 17.75, P=.033) (T2 vs. T0). Furthermore, an interaction was found for anxiety (HADS) (P=.023), with PPEP-Pituitary reporting less anxiety at T2 relative to baseline (difference -3.10, P=.007). In addition, an interaction was found for depressive symptoms (HADS) (P=.025), with PPEP-Pituitary reporting less depressive symptoms at T2 relative to T1 (difference -2.86, P=.011), as well as at T2 relative to T0 (difference -3.38, P=.009). Furthermore, an interaction was found for the Total HADS score (P=.009), with PPEP-Pituitary reporting a lower total HADS score at T2 relative to T1 (difference -5.33, P=.021), as well as lower at T2 relative to T0 (difference -6.85, P=.002). A new finding raised in this clinical sample analysis in partners was that a significant interaction was found for social functioning (SF-36) (P=.036), with PPEP-Pituitary reporting better social functioning at T2 relative to T1 (difference 19.70, P=.023), which was also significantly different from baseline (difference 22.30, P=.012).

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).

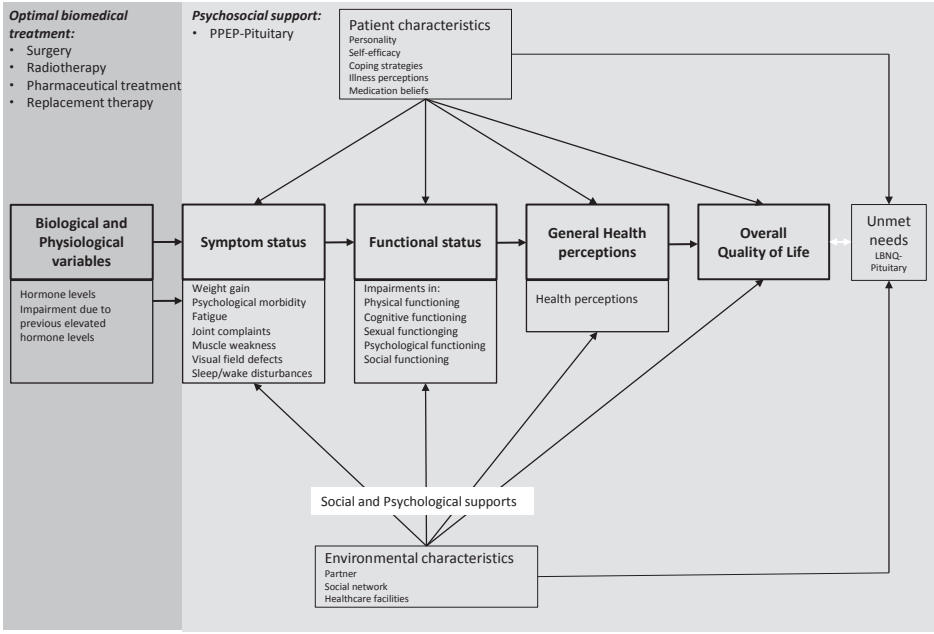

Figure 1. The Wilson and Cleary model elaborated for pituitary disease.

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 reliable 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 fasiculus 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

(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 sand 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 categorised 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 in 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) fulfil 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.

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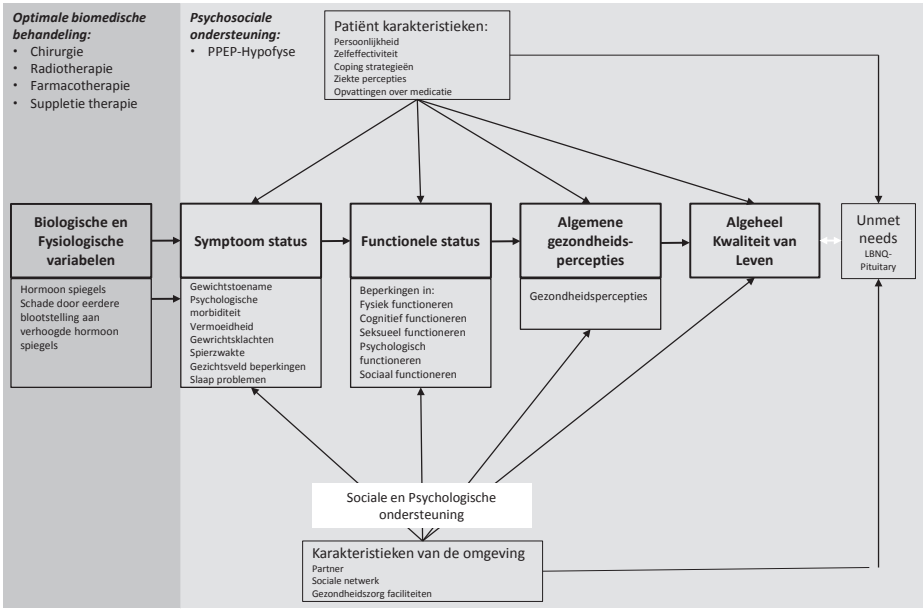
CHAPTER 16

Nederlandse samenvatting

Patiënten met een hypofyse ziekte in een stabiele medische conditie laten aanhoudende morbiditeit zien. Dit proefschrift beschrijft de gezondheidsuitkomsten van deze patiënten vanuit een biopsychosociaal model, met biologische en fysiologische uitkomstmaten aan de ene kant en maten voor de gezondheidspercepties aan de andere kant, volgens het Wilson-Cleary model (1) (Figuur 1).



Figuur 1. Wilson en Cleary model uitgewerkt voor hypofyse ziekten.

Deel I: Lange termijn effecten van de ziekte van Cushing op het menselijke brein

Bestaande literatuur over het brein van patiënten met actieve ziekte van Cushing laat zien dat er bij deze groep patiënten sprake is van een kleiner volume van de hippocampus, meer cerebrale atrofie, een kleiner volume van het cerebellum (bilateraal) en verminderde neurochemische activiteit in de frontaal kwab en de thalamus. Functionele MRI in volwassenen met actieve ziekte van Cushing waarbij gebruik werd gemaakt van een emotionele gezichten taak toonde verminderde activiteit in de linker anterieure superieure temporale gyrus en verhoogde activiteit in frontale, mediale, en subcorticale gebieden. Longitudinaal onderzoek laat zien dat na behandeling voor hypercortisolisme, het volume van de hypocampus en de neurale activiteit toeneemt en dat atrofie van het brein afneemt. Cross-sectioneel onderzoek bij patiënten na langdurige remissie van de ziekte van Cushing, laat geen verschil zien in het volume van de hypocampus tussen patiënten en gezonde controlepersonen. Echter bij de

patiënten groep was er wel sprake van een verminderde totale hoeveelheid grijze stof (corticaal en subcorticaal), een dunnere cortex en neuro-chemische afwijkingen. De gevonden veranderingen in het brein bleken geassocieerd te zijn met klinische karakteristieken (bijv. duur van blootstelling aan hypercortisolisme, plasma cortisol, cortisol in urine) en gedragsmatige uitkomsten, zoals geheugen en stemming (Functionele status) (**Hoofdstuk 2**).

In een onderzoek uitgevoerd op onze afdeling werden patiënten na langdurige remissie van de ziekte van Cushing vergeleken met controlepersonen die gelijk waren voor leeftijd, geslacht en opleidingsniveau. Dit onderzoek laat zien dat patiënten kleinere grijze stof volumes hadden in de anterieure cingulate cortex en grotere grijze stof volumes in de linker posterieure kwab van het cerebellum in vergelijking met de controlepersonen. De patiënten rapporteerden eveneens meer depressieve klachten, angst, sociale fobie, apathie en cognitieve klachten. De gevonden veranderingen in het brein waren echter niet gerelateerd aan de gerapporteerd psychologische morbiditeit (**Hoofdstuk 3**). Een functionele MRI analyse in dezelfde groep patiënten en controlepersonen laat zien dat patiënten een verminderde activiteit hadden in de ventromediale prefrontale cortex tijdens het verwerken van emotionele gezichten (i.v.m. vervormde gezichten), waarbij er geen verschil was in amygdala activiteit. Tevens laat een post-hoc analyse zien dat er een verminderde functionele koppeling was tussen de ventromedicale cortex en de posterieure cingulate cortex. Net zoals bij de observaties van hoofdstuk 3, werden er geen associaties gevonden tussen activiteit in het brein en gerapporteerd psychologische morbiditeit (**Hoofdstuk 4**). De observaties beschreven in hoofdstuk 2-4 suggereren dat de eerdere bootstelling aan hypercortisolisme mogelijk heeft geleid to veranderingen in het brein. Echter, de beschreven studies waren allen cross-sectioneel, waardoor er geen definitieve conclusie kan worden getrokken over het bestaan van een causaal verband.

Deel II: Klinische implicaties van bijnier insufficiëntie

In **Hoofdstuk 5** hebben we een nieuwe methode om cortisol te meten over een lange periode geëvalueerd. Hiervoor hebben we cortisol gemeten in hoofdhaar bij patiënten die behandeld werden voor bijnier insufficiëntie. We vonden dat patiënten met hydrocortison suppletie therapie voor bijnier insufficiëntie hogere haar cortisol niveaus hadden dan patiënten met een hypofyse ziekte zonder bijnier insufficiëntie en gezonde controlepersonen. Zoals verwacht bleek dat een hogere hydrocortison dosis geassocieerd was met hogere haar cortisol niveaus. Uit aanvullende analyses bleek dat mannen met bijnier insufficiëntie hogere haar cortisol niveaus hadden in vergelijking met vrouwen, terwijl zij dezelfde dosis gebruikten. Dit verschil tussen mannen en vrouwen werd niet gezien bij patiënten met een hypofyse aandoening zonder bijnier insufficiëntie en gezonde controlepersonen. Bij de mannelijke patiënten waren hogere haar cortisol niveaus geassocieerd met een hogere Body Mass Index (BMI). Deze observaties zouden een milde overbehandeling met hydrocortison kunnen suggereren, met name bij mannen.

In hetzelfde cohort als beschreven in hoofdstuk 5 werd vervolgens onderzocht of systemische cortisol blootstelling gemeten in hoofdhaar geassocieerd was met de door patiënten gerapporteerde kwaliteit van leven (**Hoofdstuk 6**). In dit hoofdstuk staat beschreven dat patiënten met bijnier insufficiëntie meer beperkingen in kwaliteit van leven rapporteren in vergelijking met gezonde controlepersonen. Het bleek dat een hogere hydrocortison inname was geassocieerd met meer beperkingen in kwaliteit van leven. Slechts enkele correlaties werden gevonden tussen haar cortisol niveaus en kwaliteit van leven. Deze bevindingen suggereren dat beperkingen in kwaliteit van leven bij patiënten met bijnier insufficiëntie niet *per se* gerelateerd zijn aan een hogere cortisol blootstelling als gevolg van hydrocortison suppletie therapie.

In **Hoofdstuk 7** is het cognitief functioneren onderzocht van patiënten met bijnier insufficiëntie die behandeld werden met hydrocortison suppletie therapie. De resultaten laten zien dat patiënten slechter presteerden op geheugen taken en executieve functie taken in vergelijking met gezonde controlepersonen die gelijk waren voor leeftijd, geslacht en opleiding. Bij de vergelijking tussen patiënten die hun gebruikelijke dosis hydrocortison hadden ingenomen en patiënten die hun hydrocortison inname hadden uitgesteld werd geen direct verschil in het cognitief functioneren gezien. Daarnaast was gerapporteerde psychologische morbiditeit geassocieerd met een verslechtering in het visuele geheugen en executief functioneren. In **Hoofdstuk 8** staat beschreven dat patiënten met bijnier insufficiëntie die behandeld worden met hydrocortison suppletie therapie meer psychologische morbiditeit rapporteren en meer beperkingen in kwaliteit van leven in vergelijking met gezonde controlepersonen. Er werden geen verschillen gevonden op persoonlijkheidstrekken. In overeenstemming met de resultaten beschreven in hoofdstuk 6, was een hogere hydrocortison inname geassocieerd met een hogere prevalentie van maladaptieve persoonlijkheidstrekken, meer psychologische morbiditeit en meer beperkingen in kwaliteit van leven.

Deel III: De volgende stap in het verbeteren van kwaliteit van leven bij hypofyse ziekten

Bestaande literatuur over kwaliteit van leven van patiënten met een hypofyse ziekte laat zien dat kwaliteit van leven sterk negatief beïnvloed wordt door de hypofyse ziekte, waarbij patiënten met acromegalie of de ziekte van Cushing het meest aangedaan lijken. In de literatuur wordt er gebruik gemaakt van veel verschillende vragenlijsten om kwaliteit van leven te meten. Een relatief klein aantal studies heeft interventies geëvalueerd om kwaliteit van leven te verbeteren, waaronder farmaceutische en chirurgische interventies. Het aantal studies dat kwaliteit van leven heeft onderzoek bij (nog) niet behandelde patiënten is vrij klein en slechts enkele studies hebben kwaliteit van leven onderzocht bij patiënten na langdurige follow-up. De oorzaak voor de blijvende klachten na behandeling lijkt multifactorieel te zijn, gezien de variatie aan somatische, psychologische en omgevingsfactoren die van invloed zijn op kwaliteit van leven. Een van de psychologische factoren die van invloed is op kwaliteit

van leven, is negatieve ziekte percepties (**Hoofdstuk 9**). Daarnaast is het zo dat een groot gedeelte van de patiënten met een hypofyse aandoening levenslang medicatie nodig heeft. Volgens de theorie van het 'Extended Common-Sense Model' (zie hoofdstuk 1), hebben zowel ziekte percepties, als de opvattingen over de behandeling invloed op kwaliteit van leven. In **Hoofdstuk 10** zijn daarom de opvattingen over de medicatie onderzocht bij patiënten met acromegalie. De resultaten laten zien dat sterkere opvattingen over de noodzaak van het gebruiken van somatostatine analogen geassocieerd is met het toeschrijven van meer klachten aan de ziekte, het ervaren van meer negatieve consequenties en een slechtere ziekte-specifieke kwaliteit van leven. Het hebben van meer zorgen over de mogelijke bijwerkingen van somatostatine analogen is geassocieerd met het ervaren van meer fluctuaties in de klachten.

In **Hoofdstuk 11** werd gebruik gemaakt van focus groep gesprekken om kwaliteit van leven van patiënten met een hypofyse ziekte verder in kaart te brengen. Onderwerpen die tijdens de gesprekken naar voren kwamen, die tot op heden niet in ziekte-specifieke kwaliteit van leven lijsten zijn opgenomen, waren problemen met het gezichtsveld, problemen rondom een kinderwens, angst om flauw te vallen, angst dat de hypofyse tumor weer terug komt, paniek, aanhoudende gedachten, problemen met een veranderde persoonlijkheid, boosheid, jaloezie, verdriet, frustratie, moeilijkheden bij de communicatie over de aandoening, onbegrip vanuit de omgeving en een kleiner sociaal netwerk. Factoren die mogelijk van invloed zijn op kwaliteit van leven waren minder efficiënte coping strategieën, negatieve ziekte percepties, negatieve opvattingen over de medicatie en 'unmet needs' met betrekking tot de zorg. Naast focus groep gesprekken met patiënten hebben we ook focus groep gesprekken gevoerd met partners van patiënten, omdat dit vaak de belangrijkste persoon in iemands omgeving is (**Hoofdstuk 12**). In de gesprekken met partners kwam naar voren dat zij zich zorgen maken over de hypofyse ziekte en negatieve opvattingen hebben over de medicatie. Zij ervaren uitdagingen in het omgaan met de gevolgen van de ziekte, problemen in de relatie, sociale problemen en 'unmet needs' met betrekking tot de zorg.

Op basis van de focus groep gesprekken met patiënten (Hoofdstuk 11) hebben we vervolgens een ziekte-specifieke vragenlijst ontwikkeld en geëvalueerd (**Hoofdstuk 13**). Deze vragenlijst meet in hoeverre patiënten belast worden door hun ziekte en in hoeverre zij behoefte hebben aan ondersteuning/hulp van gezondheidszorgprofessionals. Deze vragenlijst heet de *Leiden Bother and Needs questionnaire for pituitary disease (LBNQ-Pituitary)*. Deze lijst bevat 26 items en 5 subschalen; stemmingsproblemen, negatieve ziekte percepties, problemen in het seksueel functioneren, fysieke en cognitieve problemen, problemen in het sociaal functioneren. De resultaten laten zien dat de subschalen betrouwbaar zijn. De validiteit van de vragenlijst werd vastgesteld door de verkregen correlaties tussen de LBNQ-Pituitary en andere gevalideerde vragenlijsten.

Tot slot werd in hoofdstuk 14 een zelfmanagement programma voor hypofyse patiënten en hun partners ontwikkeld en geëvalueerd. Het Patiënt en Partner Educatie Programma voor

hypofyse ziekten (PPEP-Hypofyse) is gebaseerd op een gestandaardiseerd zelfmanagement programma voor patiënten en partners met verschillende chronische ziekten (PPEP4ALL) (2). De resultaten laten zien dat de stemming van patiënten die het PPEP-Hypofyse volgde na elke sessie verbeterde, behalve tijdens sessie 1. Bij de partners verbeterde de stemming alleen tijdens de laatste drie sessies. Na het volgen van PPEP-Hypofyse rapporteerden patiënten meer zelfeffectiviteit en dit was ook na 6 maanden nog steeds zichtbaar. Daarnaast rapporteerden patiënten minder belast te worden door stemmingsproblemen direct na PPEP-Hypofyse, maar na 6 maanden keerde dit weer terug naar het begin niveau. Na PPEP-Hypofyse rapporteerden partners meer vitaliteit en dit effect was na 6 maanden nog steeds zichtbaar. Daarnaast geven partners 6 maanden na PPEP-Hypofyse aan minder depressieve klachten te hebben en meer controle over de behandeling te ervaren.

Slotopmerkingen

Dit proefschrift beschrijft de gezondheidsuitkomsten van hypofyse ziekten vanuit een biopsychosociaal benadering. Uit de studies beschreven in dit proefschrift kunnen we concluderen dat:

- Patiënten na langdurige remissie van die ziekte van Cushing structurele en functionele veranderingen hebben in het brein die gepaard gaan met psychologische morbiditeit.
- Patiënten die behandeld worden met hydrocortison voor bijnier insufficiëntie worden blootgesteld aan verhoogde systemische cortisol niveaus zoals cortisol niveaus gemeten in hoofdhaar.
- Mannelijke patiënten die behandeld worden met hydrocortison voor bijnier insufficiëntie hebben hogere haar cortisol niveaus dan vrouwelijke patiënten terwijl zij dezelfde dosis gebruiken.
- Patiënten die behandeld worden met hydrocortison voor bijnier insufficiëntie psychologische morbiditeit rapporteren en beperkingen in kwaliteit van leven.
- In patiënten met bijnier insufficiëntie zijn beperkingen in kwaliteit van leven geassocieerd met een hogere hydrocortison inname en worden minder gereflecteerd door cortisol niveaus gemeten in hoofdhaar.
- Patiënten die behandeld worden met hydrocortison voor bijnier insufficiëntie laten milde cognitieve beperkingen zien in het geheugen en executief functioneren.
- Bij patiënten met bijnier insufficiëntie een hogere hydrocortison inname geassocieerd is met meer psychologische morbiditeit, meer maladaptieve persoonlijkheidstrekken en meer beperkingen in kwaliteit van leven.
- Patiënten met een hypofyse ziekte rapporteren beperkingen in kwaliteit van leven, die verbeteren na behandeling, maar niet lijken te normaliseren.

- Meer zorgen en sterke opvattingen over de noodzaak van medicatie in patiënten met acromegalie zijn geassocieerd met negatieve ziekte percepties en slechtere ziekte-specifieke kwaliteit van leven.
- Partners van patiënten met een hypofyse ziekte rapporteren een negatieve impact op hun dagelijks leven.
- Patiënten rapporten meer zelfeffectiviteit na het volgen van PPEP-Hypofyse.
- Partners van patiënten rapporteren een positief effect op aspecten van hun kwaliteit van leven na het volgen van PPEP-Hypofyse.

De studies beschreven in dit proefschrift laten zien dat ondanks dat patiënten in een stabiele medische conditie zijn, er gezondheidskwesties kunnen zijn op elk niveau van het Wilson-Cleary model (1). Door gebruik te maken van dit model wordt inzichtelijk dat de aanhoudende klachten verklaard en/of veroorzaakt kunnen worden door problemen in elke stadium van dit model. Hiermee geeft het ook inzicht in de grote variatie aan klinische uitkomsten tussen patiënten, waarbij sommige patiënten bijna dagelijks te kampen hebben met ernstige beperkingen, terwijl anderen dit niet ervaren of slechts licht zijn aangedaan. Het benadrukt dat een verbetering in kwaliteit van leven bij patiënten met een hypofyse ziekte optimale biomedische behandeling vraagt om zo de cascade aan verbeteringen in gezondheidsuitkomsten in gang te zetten. Verdere verbetering in kwaliteit van leven kan worden bevorderd door een hypofyse-specifiek zorgpad, waar PPEP-Hypofyse deel van uitmaakt. Op deze manier kunnen zowel karakteristieken van patiënt, als van de (gezondheidszorg) omgeving positief worden beïnvloed, met het uiteindelijke doel kwaliteit van leven van patiënten met een hypofyse ziekte te optimaliseren.

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ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
ACRO	Acromegaly
ADH	Anti-diuretic hormone
BMI	Body Mass Index
CD	Cushing's disease
CS	Cushing's syndrome
$CORT_{hair}$	Hair cortisol levels
CSM	Common-Sense Model
CRH	Corticotropin-releasing hormone
DTI	Diffusion tensor imaging
fMRI	Functional magnetic resonance imaging
FSH	Follicle-stimulating hormone
GH	Growth hormone
GHD	Growth hormone deficiency
GHRH	Growth hormone releasing hormone
GnRH	Gonadotropin-releasing hormone
HPA-axis	Hypothalamic-pituitary-adrenal-axis
IGF-1	Insulin-like growth factor-1
LBNQ-Pituitary	Leiden Bother and Needs Questionnaire for Pituitary disease
LH	Luteinising hormone
MRI	Magnetic resonance imaging
NFA	Non-functioning pituitary adenoma
PAI	Primary adrenal insufficiency
PPEP-Pituitary	Patient and Partner Education Program for Pituitary disease
PRL	Prolactinoma
PRO	Patient reported outcome
PROM	Patient reported outcome measure
QoL	Quality of life
SAI	Secondary adrenal insufficiency
SMI	Self-management intervention
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone
VAS	Visual Analogue Scale
VBM	Voxel-based morphormetry
vmPFC	Ventromedial prefrontal cortex

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1. **Andela CD***, van der Werff SJ*, Pannekoek JN, van den Berg SM, Meijer OC, van Buchem MA, et al. Smaller grey matter volumes in the anterior cingulate cortex and greater cerebellar volumes in patients with long-term remission of Cushing's disease: a case-control study. *Eur J Endocrinol 2013;169(6):811-9.*

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CURRICULUM VITAE

Cornelie Duifke Andela werd geboren op 25 mei 1989 te Mons (België). Zij groeide op in Scheveningen waar zij in 2007 haar Gymnasium diploma behaalde aan het Vrijzinnig Christelijk Lyceum. In datzelfde jaar begon zij met de studie Psychologie aan de Universiteit van Leiden. Tijdens haar Master Klinische Neuropsychologie liep zij stage op de afdeling Ouderengeneeskunde van het Bronovo ziekenhuis in Den Haag en deed zij haar wetenschapsstage bij de afdeling Endocrinologie van het Leids Universitair Medisch Centrum (LUMC). In 2011 studeerde zij af, waarna zij vrijwel direct startte met haar promotieonderzoek bij de afdeling Endocrinologie van het LUMC onder leiding van Dr. N.R. Biermasz, Prof. A.A. Kaptein en Prof. A.M. Pereira. Zij presenteerde de onderzoeksresultaten op verschillende nationale en internationale congressen. Hiervoor werden haar enkele reisbeurzen toegekend. De resultaten van dit onderzoek staan beschreven in dit proefschrift. In 2015 is zij naast de afronding van haar promotieonderzoek begonnen met de studie Geneeskunde aan de Universiteit van Leiden. Per september 2017 zal zij beginnen met haar coschappen aan het LUMC.

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