Pituitary diseases

Long-term psychological consequences

Jitske Tiemensma

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Chapter 1

General Introduction

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1. Introduction

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

2. The neuroendocrine system: an overview

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

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

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

Adrenocorticotropic hormone and the HPA-axis

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

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

Growth hormone

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

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

3. Pituitary adenomas

Cushing's disease

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

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

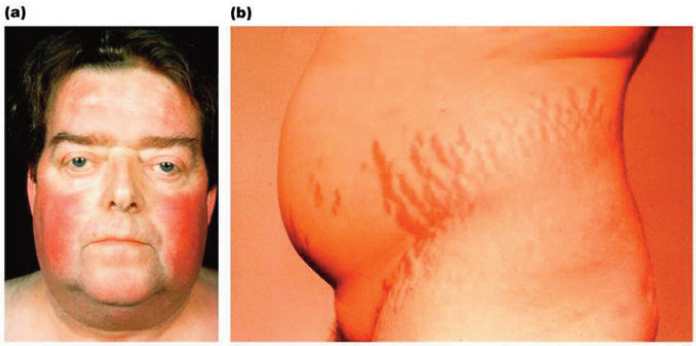

Figure 1. *Common clinical features in Cushing's disease, adapted from Pearson Education, Inc. 2007, publishing as Benjamin Cummings.*

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

Acromegaly

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

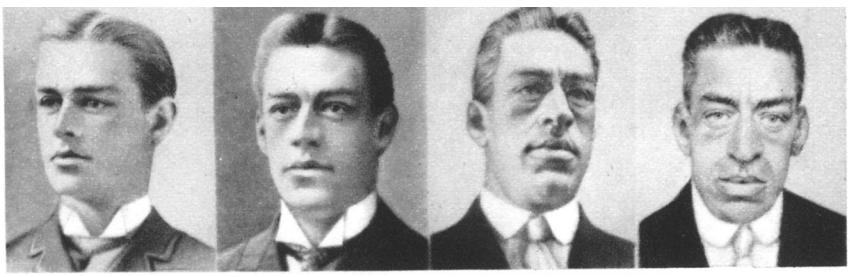

Figure 2. *Features of acromegaly over time, adapted from Chauvet, 1935.*

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

Non-functioning pituitary macroadenoma

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

4. Illness perceptions

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

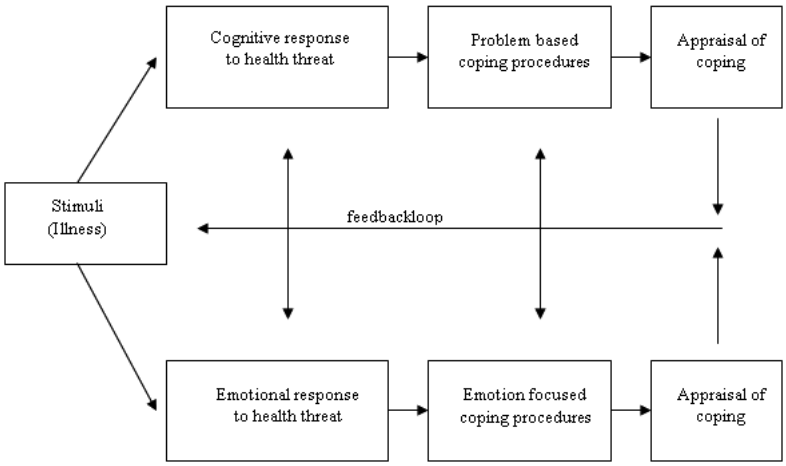

Figure 3. *The parallel process model (CSM), adapted from Leventhal et al., 2003 (31).*

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

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

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

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

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

5. Quality of life and psychological functioning

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

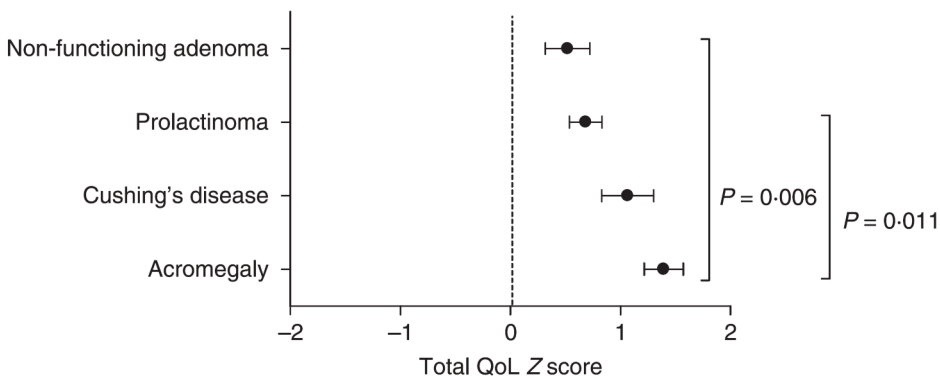

Figure 4. *Quality of life in pituitary adenomas (higher Z-score represents a worse QoL), adapted from Van der Klaauw et al., 2008 (45).*

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

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

Psychological functioning in Cushing's disease

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

Psychological functioning in acromegaly

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

6. Scope of the present thesis

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

Illness perceptions and coping strategies

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

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

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

The prevalence of cognitive impairment and psychopathology

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

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

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Chapter 2

Negative illness perceptions are associated with impaired quality of life in patients after long-term remission of Cushing's syndrome

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Abstract

Objective: Illness perceptions pertain to the pattern of beliefs patients develop about their illness. Illness perceptions are determinants of quality of life (QoL). Factors contributing to persisting impaired QoL after Cushing's syndrome (CS) remain largely unknown. Therefore, the objective of the current study was to explore illness perceptions, as potentially modifiable psychological factors, in relation to QoL in patients with long-term remission of Cushing's syndrome.

Design: This was a cross-sectional study.

Methods: We included patients with long-term remission of CS (n=52). Illness perceptions were evaluated using the Illness Perception Questionnaire-Revised (IPQ-R), and QoL was measured using the physical symptom checklist, EuroQoL-5D, and the CushingQoL. Reference data were derived from recent studies and included patients with vestibular schwannoma (n=80), acute (n=35) or chronic (n=63) pain, and chronic obstructive pulmonary disease (COPD; n=171).

Results: Illness perceptions showed a strong correlation with QoL. Patients with CS scored distinctively more negative on the IPQ-R compared with patients with vestibular schwannoma and patients with acute pain, and also reported more illness related complaints (all $P<0.01$). There were also some differences in illness perceptions between patients with CS and patients with chronic pain and patients with COPD, but there was no distinct pattern.

Conclusions: Patients after long-term remission of CS report more negative illness perceptions compared with patients with other acute or chronic conditions. Further research is needed to assess whether QoL in CS can be improved by addressing these illness perceptions, for example, by a self-management intervention program.

Introduction

Cushing's syndrome is characterized by excessive glucocorticoid levels, mostly caused by ACTH-producing pituitary adenomas, but in one third of the cases by ectopic ACTH-producing neuroendocrine tumors or by adrenal adenomas/carcinomas. Following successful treatment of hypercortisolism, signs and symptoms improve substantially. However, prolonged, excessive exposure to glucocorticoids may have long-lasting adverse effects on behavioral and cognitive functions, due to functional and structural alterations in specific brain target areas (1-4). Furthermore, these patients do not completely return to their premorbid level of functioning, and quality of life (QoL) is persistently impaired despite long-term cure of Cushing's syndrome (5). Although the decreased QoL may originate from persisting limitations due to irreversible effects of excessive glucocorticoid exposure, an alternative hypothesis is that the psychological impact of suffering from this disease results in QoL reduction. We recently reported that coping strategies are indeed ineffective in patients with pituitary disease (6). Persistent inappropriate thoughts about the disease and/or its treatment can influence general well-being. Patients and their doctors may have (totally) discrepant perceptions of the severity of the disease and the success of treatment. This concept has not been elaborated for endocrine diseases and can be studied by measuring illness perceptions.

Illness perceptions pertain to the way patients make sense of, and respond to, their illness. Illness perceptions are conceptualized in the common sense model (CSM) of self-regulation. The CSM explains how patients generate both cognitive representations of, and emotional reactions to, their illness, integrating internal and external stimulus information with their pre-existing illness-theory (7). Leventhal *et al.* (8) designed the CSM which starts from the premise that individuals are active problem solvers, who make sense of a threat to their health by developing a cognitive representation of the threat, which determines how the individual responds. Patients cluster these representations or ideas about the illness around five cognitive components: 1) identity: the label that is used by the individual to describe the condition and the associated symptoms; 2) cause: personal ideas about the cause of the condition; 3) time-line: expectations about the likely duration of the condition; 4) consequences: the physical, psychological, and social effects of the condition; 5) cure/control: the extent to which the condition is amenable to cure and/or control. These components form the illness representations, which determine the patient's coping procedures (9). The source of patient's perceptions is diverse. It can be based on information from doctors, relatives, friends, or media, but also from first hand experience with someone in the close proximity who suffers from an illness. Therefore, patients' illness per-

ceptions are subjective, may be partly or completely incorrect, and do not necessarily represent the medical status of the disease.
At present, there are no studies that have evaluated illness perceptions in patients with long-term remission of Cushing's syndrome. Therefore, the aim of the present study is to explore the illness perceptions of patients after long-term remission of Cushing's syndrome in relation to reported QoL using the Illness Perception Questionnaire-Revised (IPQ-R) and several QoL questionnaires. The IPQ-R questionnaire assesses perceptions on each of the five components by asking the patient for their own beliefs about the Cushing's syndrome. Since there are no previous studies in endocrine patients we compared findings to several Dutch reference groups.

Patients and Methods

Patients

Cushing's syndrome had been diagnosed based on internationally agreed guidelines, i.e. the clinical manifestations and positive biochemical tests including increased urinary excretion rates of free cortisol, decreased overnight suppression by dexamethasone (1mg) and, since 2004, elevated midnight salivary cortisol values. All patients had been treated by transsphenoidal surgery or adrenalectomy, if necessary followed by repeated surgery and/or postoperative radiotherapy. Cure of Cushing's syndrome was defined by normal overnight suppression of plasma cortisol levels (<50nmol/l) after administration of dexamethasone (1mg) and normal 24h urinary excretion rates of cortisol (<220nmol/24h). Hydrocortisone independency was defined as a normal cortisol response to CRH or insulin-tolerance test (ITT).
All patients were followed at our outpatient department. Patients were monitored for (recurrence of) disease, according to appropriate dynamic tests. 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, confirmed by ITT or CRH test, the average dose of hydrocortisone was 20mg/d divided into two to three dosages. Evaluation of GH deficiency was performed by ITT and/or GHRH-arginine test, only in patients under the age of 70yr and only after at least 2yr of remission. Somatotrope insufficiency was treated with rhGH replacement, aiming at IGF-I concentrations in the normal range for age. In addition, free T_4 and testosterone levels (in male patients) were assessed. If results were below the lower limit of the respective reference ranges, substitution with L-T_4 and/or testosterone was prescribed. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replace-

ment was provided. Progesterone replacement was also provided to women with an intact uterus.
Education level was based on the Dutch education system, which is comparable to the International Standard Classification of Education. Low education level was defined as primary education to lower secondary education. Medium education level incorporated (upper) secondary education to post-secondary non-tertiary education, while high level education was defined as the first stage of tertiary education to the second stage of tertiary education.
Inclusion criteria for this study were age over 18yr and remission defined by strict biochemical criteria for at least 1yr. The protocol was approved by the LUMC Medical Ethics Committee.

Protocol

We performed a clinical chart review of 77 patients with Cushing's syndrome. All were in remission at the time of the current study for at least 1yr. The long-term treatment outcome of these patients has been characterized and described in detail (10). We invited these patients to participate in the current study. Twenty-five patients (32%) refused to participate, and 52 patients (68%) participated in the current study and completed all questionnaires. The clinical characteristics of the subjects who did not participate, did not differ from those of the participants. Patients were asked to complete questionnaires on illness perceptions and QoL at home and return these questionnaires in a prepaid envelope.

Illness Perception Questionnaire-Revised (IPQ-R)

The IPQ-R was used to measure cognitive and emotional representations of Cushing's syndrome (11;12). The questionnaire was developed to assess the components of the illness representation of Leventhal's Self-Regulatory Model and is frequently used to study illness perceptions in chronic conditions (13-17). The IPQ-R is divided into three sections. The first part consists of the illness identity dimension, with a list of 14 general commonly occurring symptoms and 13 symptoms commonly occurring in Cushing's syndrome. Patients are asked to rate whether or not they experienced the symptoms, and if they believe the symptom to be related to Cushing's syndrome (yes/no). The summed up yes-rated items of the disease-related symptoms were 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 five-point Likert scale (from strongly disagree to strongly agree). The questions were 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), consequences (negative consequences of the disease),

emotional representations (the likelihood to seek medical care), personal control (perceived personal controllability of the disease), treatment control (perceived treatment controllability of the disease), 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 was about the causal attributions. This section consists of 18 statements concerning possible causes that patients considered that contributed to their disease, scored on a five-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 (11). The analysis produced 4 factors accounting for 72% of the variance. The first factor labeled psychological attributions accounted for 31% of the variance and consisted of the items emotional state, personality, overwork, stress or worries, mental attitude, family problems/worries, ageing, altered immunity, and own behavior. The second factor labeled risk factors accounted for 22% of the variance and consisted of the items pollution in environment, diet or eating habits, bacteria or virus, accident/injury, and poor medical care. The third factor behavioral attributions accounted for 11% of the variance and consisted of the items smoking and alcohol use. The fourth factor chance accounted for 9% of the variance and consisted of the items hereditary and chance/bad luck. This fourth factor demonstrated insufficient internal reliability ($\alpha<0.50$), and was excluded from further analysis. Higher scores on the other three causal subscales indicate stronger beliefs in those attributions in causing Cushing's syndrome.

Quality of life questionnaires

Physical symptoms checklist: This is a checklist of 55 physical symptoms that are mentioned in the DSM-III classification (18). The symptoms cover most organ systems. There are 11 general/ neurological items, 10 autonomic items, 8 musculoskeletal/pain items, 13 gastrointestinal items, 5 genital items and 4 items about feeling hot/cold. 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 (19).
EuroQoL-5D: This QoL questionnaire measures five health dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores are expressed on a 1-3 scale per dimension, with a higher score indicating a 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 QoL state (20). The VAS score

ranges from 0 to 100, with higher scores indicating a better QoL.
CushingQoL: This is a disease specific QoL questionnaire specifically designed to assess QoL in patients with Cushing's syndrome. The questionnaire consists of 12 questions on a five-point Likert scale ranging from always to never. The total score ranges from 12 to 60, with a lower score indicating a greater impact on health related QoL (21).
Three patients did not complete all QoL questionnaires.

Reference populations

Since the general population is not assumed to have an illness, there are no normative values of the IPQ-R available for the general population. Scores of patients with acute and chronic pain may be used instead (22). The other reference groups were chosen based on available data of the IPQ-R in Dutch samples.
Patients with acute and chronic pain are described in the paper that presents the revised version of the IPQ (11). The reference group with acute pain consisted of 35 subjects who were recruited from a private practice for physical therapy (20 men, 15 women, mean age of 36±12yr). The patients presented with a first-time peripheral painful injury that had been present for less than six weeks. The reference group of patients with chronic pain consisted of 63 subjects (26 men and 37 women, with a mean age of 54±11yr) who were recruited from hospital based chronic pain clinics. All patients experienced pain for longer than 3 months that was unexplained by medical signs alone.
The third reference group consisted of 171 Dutch patients (112 men and 59 women, mean age 66±10yr) suffering from chronic obstructive pulmonary disease (COPD) (23). A chest physician diagnosed all patients as suffering from emphysema and/or chronic bronchitis.
The fourth reference group consisted of 80 patients with vestibular schwannoma who just had been told the diagnosis, but who had not received a treatment proposal at the time of the study (36 men, 43 women, and one anonymous responder. Mean age 57yr, range 26-79yr) (22). Thirty-eight percent of the patients suffered from an intracanalicular tumor, and 8% from a cystic component. The symptoms experienced by these patients included tinnitus, unsteadiness, vertigo, headache, and earache.

Statistical analysis

Data were analyzed using PASW Statistics version 17.0.2 (SPSS Inc., Chicago, IL, USA). All data were presented as mean ± standard deviations, unless mentioned otherwise. The primary analysis comprised the relationship between illness perceptions and QoL. Partial correlations were calculated controlling for duration of remission. The level of significance for this analysis was set at $P \leq 0.05$. The com-

parison of patients with a relatively better QoL and patients with a worse QoL consisted of a Student's t-test with the level of significance set at P≤0.01, because of multiple comparisons. The possible effects of duration of remission and duration of follow-up were explored by linear regression analysis. The standardized β coefficients of this analysis were reported.
Secondary analysis comprised the comparison of results in patients with long-term cure of Cushing's syndrome and of results in various reference groups. Means were calculated for all subscales of the IPQ and compared between groups using Student's t-test. Patients with cure of Cushing's syndrome with and without hydrocortisone substitution were also compared using a Student's t-test, while the different treatment modalities were compared using an ANOVA with a *post hoc* analysis when appropriate. Since multiple comparisons were used, the level of significance was set at P≤0.01.

Results

Sociodemographic and clinical characteristics

Clinical characteristics of the patients are detailed in Table 1. Forty-six patients (88%) had pituitary ACTH-dependent hypercortisolism, and 6 patients (12%) had Cushing's syndrome due to adrenal tumor. There were no significant differences between patients who had been treated for Cushing's syndrome caused by an adrenal cortisol producing tumor and patients who had been treated for Cushing's disease on the IPQ-R, nor on any of the QoL questionnaires.
Thirty-four patients (65%) had been treated by transsphenoidal surgery, seven patients (14%) by both transsphenoidal surgery and adrenalectomy and 11 patients (21%) had been treated by adrenalectomy. Fourteen patients (27%) had been treated by additional pituitary irradiation for persistent disease after surgery. At the time of this study, all patients were in remission and the mean duration of remission was 16±12yr (range 2-46yr). Twenty-three patients were GH deficient, of whom 21 received GH therapy. A total of 32 patients (62%) were treated for some degree of pituitary insufficiency, and 30 patients (58%) were substituted with hydrocortisone. Figure 1 shows the self-reported symptoms of various organ systems in patients after long-term remission of Cushing's syndrome. Most complaints involved musculoskeletal pain.

Illness perceptions in Cushing's syndrome as measured with the IPQ-R

Illness identity dimension

More than half of the patients reported to suffer from symptoms like gaining weight, less muscle strength, less energy, concentration problems, memory im-

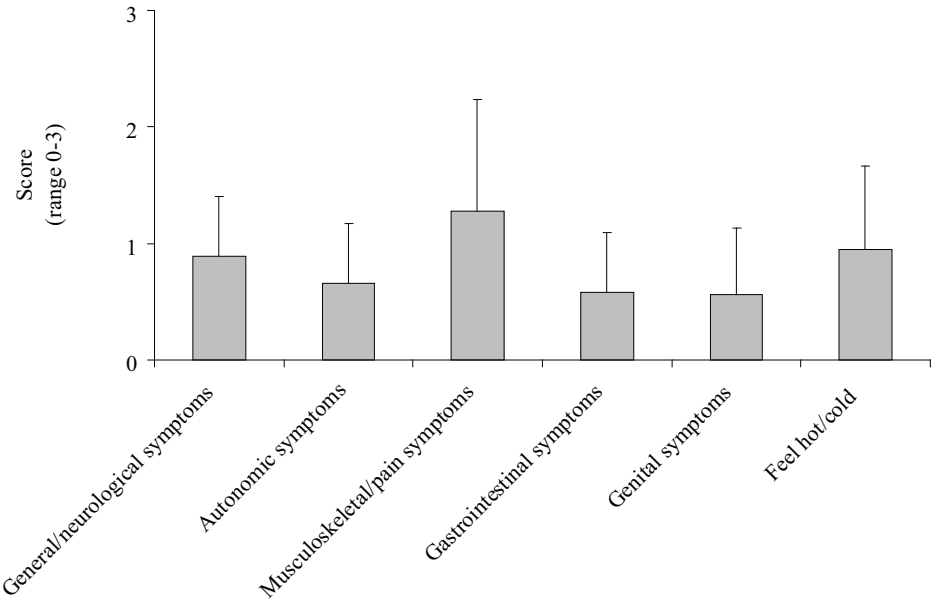

Figure 1. *Scores of patients after long-term remission of Cushing's syndrome on the various organ systems*

Table 1 Clinical characteristics

	Total sample of patients with Cushing's syndrome (n=52)	**Hydrocortisone dependent (n=30)**	**Not hydrocortisone dependent (n=22)**
Gender (male/female)	7/45	5/25	2/20
Age in yrs	54 (11)	53 (11)	55 (11)
Educational level (n)	Low: 16 (31%) Medium: 18 (35%) High: 16 (31%) Unknown: 2 (4%)	Low: 9 (30%) Medium: 11 (37%) High: 9 (30%) Unknown: 1 (3%)	Low: 7 (32%) Medium: 7 (32%) High: 7 (32%) Unknown: 1 (5%)
Transspenoidal surgery, n (%)	41 (79%)	16 (53%)	18 (82%)
Adrenal surgery, n (%)	11 (21%)	7 (23%)	4 (18%)
Transspenoidal and adrenal surgery, n (%)	7 (14%)	7 (23%)	0 (0%)
Postoperative radiotherapy, n (%)	14 (27%)	10 (33%)	4 (18%)
Duration of remission in yrs	16 (12)	18 (13)	14 (10)
Duration of follow-up in yrs	17 (12)	18 (13)	15 (10)
Hypopituitarism, n (%)	Any axis: 32 (62%) GH: 23 (44%) LH/FSH: 14 (27%) TSH: 19 (37%) ADH: 8 (15%)	Any axis: 30 (100%) GH: 21 (70%) LH/FSH: 13 (43%) TSH: 17 (57%) ADH: 8 (27%)	Any axis: 2 (9%) GH: 2 (9%) LH/FSH: 1 (5%) TSH: 2 (9%) ADH: 0 (0%)
HC substitution, n(%)	30 (58%)	30 (100%)	0 (0%)

Data are mean ± SD or number and %; HC, hydrocortisone

Table 2. Symptoms related to Cushing's syndrome

Symptoms	Cushing's syndrome, n=52
Less muscle strength	35 (67%)
Less energy	30 (58%)
Gaining weight	28 (54%)
Concentration problems	28 (54%)
Vulnerable skin	27 (52%)
Memory impairment	27 (52%)
Sore joints	25 (48%)
Bad physical condition	22 (42%)
Muscle pain	19 (37%)
Slow wound healing	19 (37%)
Visual impairment	13 (25%)
Hair growth	13 (25%)
Hair loss	9 (17%)

Data are n (%), from the dimension 'illness identity' of the IPQ-R

pairment, and vulnerable skin and believed that these symptoms are solely caused by Cushing's syndrome (Table 2).

Causal attributions dimension

In the last part of the questionnaire, patients after remission of Cushing's syndrome reported relatively frequently psychological attributions as their perceived cause of Cushing's syndrome. Risk factors and behavioral attributions were infrequently mentioned as being the cause of their illness.

Illness perception dimensions

There were no differences in the IPQ-R dimensions between patients who had been treated by different treatment modalities (i.e. transsphenoidal surgery *versus* both transsphenoidal surgery and adrenalectomy *versus* adrenalectomy, and secondly additional radiotherapy *versus* no additional radiotherapy).

When using a linear regression model, gender and age were not associated with any of the illness perception dimensions. Duration of remission was also not associated with any of the illness perception dimensions, except for illness coherence, which constitutes the personal understanding of the disease (β=-2.698, P=0.04). Furthermore, there were differences between patients with hydrocortisone substitution (n=29) and patients without cortisol substitution (n=23) in the perceived chronicity (P=0.005) and fluctuations in the disease (P=0.002). The clinical characteristics of patients with and without hydrocortisone substitution are detailed in Table 1.

In addition, hypopituitarism was associated with the number of symptoms attributed to the disease (β=0.303, P=0.030), chronicity (β=0.468, P=0.001) and fluctuations (β =0.333, P=0.016) of the disease, and the perceived consequences (β=0.323, P=0.019).

Relationship between illness perceptions and QoL

The scores of patients with Cushing's syndrome on the various QoL questionnaires are depicted in Table 3. Levels of association between the IPQ-R dimensions and the QoL scales are shown in Table 4 as partial correlations, controlled for duration of remission.

The IPQ-R dimension illness identity showed positive correlations with the physical symptoms checklist (PSC), mobility, activity, and anxiety, and inverse correlation with the VAS and the CushingQoL, all reflecting worse QoL when more symptoms are attributed to the disease on the illness identity dimension. The dimension timeline (acute/chronic) also showed an inverse correlation with the VAS and the CushingQoL. This indicates that patients who perceive their disease as chronic have a lower QoL. The dimension negative consequences showed a positive correlation with activity, and a negative correlation with the VAS and the CushingQoL. Furthermore, the emotional representations dimension showed a positive correlation with the PSC, mobility, and anxiety and an inverse correlation with the CushingQoL. The dimension personal control showed an inverse correlation with self-care and a positive correlation with the VAS. Perceived treatment control showed an inverse correlation with mobility and pain, and a positive correlation with the VAS and the CushingQoL. The dimension illness coherence (understanding of the disease) also showed an inverse correlation with mobility. Lastly, psychological attributions as a cause of Cushing's syndrome showed a positive correlation with the PSC and mobility, but an inverse correlation with the CushingQoL. The dimensions timeline (cyclical), risk factors, and behavioral attributions did not correlate with any of the QoL questionnaires.

In addition, patients with low scores and patients with high scores on the various QoL questionnaires were compared. The median value was used to define low

Table 3 QoL in patients with Cushing's syndrome

	Cushing's syndrome, n=49
Physical Symptoms Checklist	
Total Score	40.8 (26)
EuroQoL-5D	
Mobility	1.4 (1)
Self-care	1.1 (0)
Activity	1.7 (1)
Pain	1.8 (1)
Anxiety	1.4 (1)
VAS	65.5 (18)
Cushing QoL	
Total Score	52 (18)

Data are mean (SD). A higher score on the PSC, mobility, self-care, activity, pain, and anxiety indicates a worse QoL, whereas higher scores on the VAS and the CushingQoL indicate a better QoL.

Table 4 Partial correlations between the IPQ-R dimensions and QoL scales, controlling for duration of remission

	Physical symptoms checklist	EQ-5D Mobility	EQ-5D Self-care	EQ-5D activity	EQ-5D pain	EQ-5D Anxiety	EQ-5D VAS	Cushing QoL
Illness identity	.625 **	.327 *		.329 *		.319 *	-.382 *	-.659 **
Timeline (acute/chronic)							-.326 *	-.339 *
Timeline (cyclical)								
Consequences				.317 *			-.411 **	-.316 *
Emotional representations	.413 **	.313 *				.591 **		-.629 **
Personal control			-.348 *				.347 *	
Treatment control		-.348 *			-.412 **		.486 **	.326 *
Illness coherence		-.353 *						
Psychological attributions	.412 **	.336 *						-.327 *
Risk factors								
Behavioral attributions								

Only correlations that reached statistical significance ($p<0.05$) are depicted, * $p<0.05$, ** $p<0.01$

versus high scores. Patients with high scores on the PSC (indicating a more impaired QoL, n=25) attributed significantly more symptoms to Cushing's syndrome (P=0.002) than patients with a lower score (n=24).
On the VAS, patients with a lower score (indicating a more impaired QoL, n=25) attributed more symptoms to Cushing's syndrome (P=0.010) than patients with a higher score (n=24). Patients with a lower score on the CushingQoL (indicating a more impaired QoL, n=23) attributed more symptoms to Cushing's syndrome (P<0.001), scored higher on timeline acute/chronic (P=0.004), higher on consequences (P<0.001), higher on treatment control (P=0.010), and lower on emotional representations (P<0.001). These analyses indicate that patients with a worse QoL report more affected illness perceptions than patients with a better QoL.
There were no significant differences in QoL between patients with and without hydrocortisone substitution (data not shown).
The above mentioned findings make clinical sense, in that the IPQ dimensions and the closely related QoL subscales measure the same concepts or concepts that logically interact with each other, i.e. disease related symptoms and daily activities, or (negative) consequences and perceived well-being.

Illness perceptions in Cushing's syndrome compared with reference groups

Illness perceptions in patients after long-term cure of Cushing's syndrome compared with acute and chronic pain patients

Illness perceptions of patients with Cushing's syndrome were compared with acute pain patients (Table 5, Figure 2). Patients with Cushing's syndrome reported more illness related complaints (P=0.008), more chronicity and fluctuations in the disease (both P<0.0001), perceived more negative consequences of the disease, and less personal (P<0.0001) and treatment (P=0.002) control. However, patients with Cushing's syndrome had a better personal understanding of the disease (P<0.0001) than patients with acute pain.
In comparison with chronic pain patients, patients with Cushing's syndrome reported less illness related complaints (P=0.003), perceived less negative consequences of the disease (P<0.001), and reported a smaller likelihood to seek medical care (P<0.0001). Patients with Cushing's syndrome reported more treatment control (P=0.002) and had a better personal understanding of the disease (P<0.0001) than patients with chronic pain.

Illness perceptions in patients after long-term cure of Cushing's syndrome compared with patients with a chronic disease

Illness perceptions of patients with Cushing's syndrome were also compared with patients with another chronic disease, i.e. COPD (Table 5). Patients with Cushing's syndrome reported less illness related complaints (P<0.001), less chronicity

Table 5 Comparison of Cushing's syndrome patients' IPQ-R scores to other populations

IPQ-R	Cushing's syndrome n=52	Acute pain n=35	Chronic pain n=63	Chronic obstructive pulmonary disease (COPD) n=171	Vestibular schwannoma n=80
Illness identity	**3.8 (3)**	2.8 (2)*	6.2 (3)*	5.6 (3)**	2.2 (2)*
Timeline (acute/chronic)	**23.6 (7)**	13.4 (5)**	23.1 (4)	26.7 (4)*	20.6 (4)*
Timeline (cyclical)	**11.9 (4)**	9.4 (3)**	12.9 (4)	12.1 (5)	10.6 (4)
Consequences	**20.4 (5)**	14.2 (4)**	23.5 (4)**	19.3 (6)	16.4 (2)**
Emotional representations	**15.3 (5)**	16.1 (4)	19.8 (4)**	14.1 (7)	15.3 (4)
Personal control	**16.9 (6)**	22.9 (4)**	18.4 (4)	22.4 (6)**	19.1 (3)*
Treatment control	**16.7 (5)**	19.4 (3)*	14.2 (3)*	14.3 (4)*	16.9 (3)
Illness coherence	**17.0 (3)**	9.3 (3)**	13.4 (5)**	NA	18.1 (4)
Psychological attributions *(score range 9-45)*	**17.9 (8)**	NA	NA	NA	NA
Risk factors *(score range 5-25)*	**8.3 (4)**	NA	NA	NA	NA
Behavioral attributions *(score range 2-10)*	**2.9 (1)**	NA	NA	NA	NA

Data are mean (SD), * $p<0.01$ compared to patients with Cushing's syndrome, ** $p<0.001$ compared with patients with Cushing's syndrome, NA: not available or not applicable

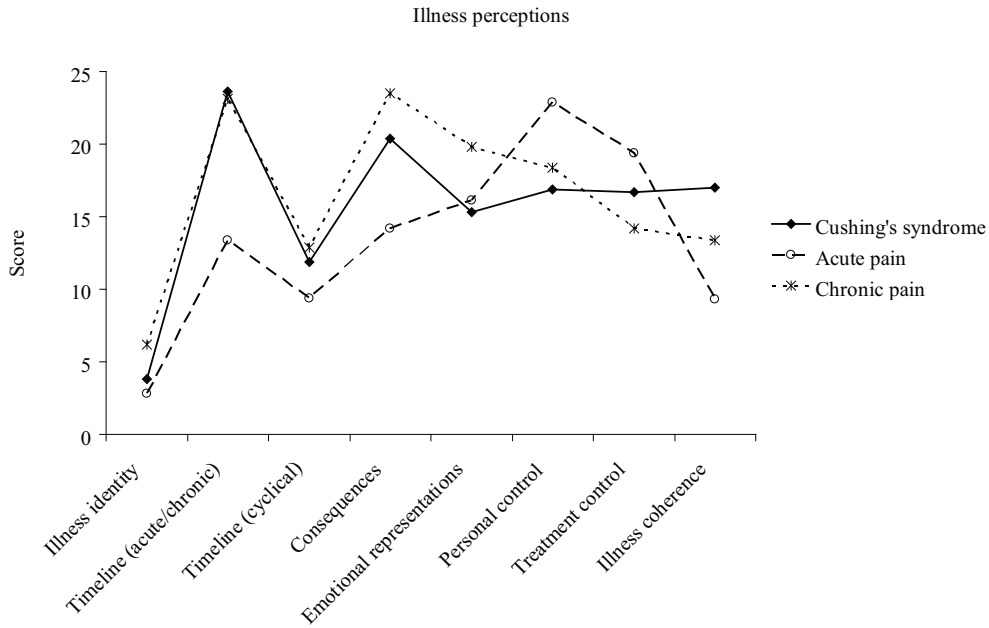

Figure 2. *Distribution of IPQ-R scores of patients after long-term remission of Cushing's syndrome, patients with acute pain, and patients with chronic pain.*

in the disease (P=0.002), and more perceived more treatment controllability (P=0.001). However, patients with Cushing's syndrome perceived less personal controllability of the disease (P<0.0001) than COPD patients.

Illness perceptions in patients after long-term cure of Cushing's syndrome compared with reference populations with vestibular schwannoma

Illness perceptions of patients with Cushing's syndrome were compared with patients suffering from untreated vestibular schwannoma (Table 5). Patients with Cushing's syndrome reported more illness-related complaints (P=0.002) and more chronicity in the disease (P=0.004). Furthermore, patients with Cushing's syndrome reported more negative consequences of the disease (P<0.0001) and perceived less personal control of the disease (P=0.010) than patients with vestibular schwannoma.

Discussion

This study was performed to assess the illness perceptions of patients after long-term remission of Cushing's syndrome in relation to QoL parameters. This is the first time that this is addressed in endocrine diseases. The results indicate that affected illness perceptions and reduced QoL parameters are strongly related. Moreover, patients after long-term remission of Cushing's syndrome report more negative illness perceptions compared with several reference groups.

This explorative study demonstrates that patients in long-term remission after treatment for Cushing's syndrome attribute more symptoms to (the aftermath of) their disease than patients with acute pain or vestibular schwannoma, but less than patients with chronic pain or COPD. Furthermore, patients with long-term cure of Cushing's syndrome show more strongly held beliefs regarding the chronic nature of the condition compared with patients with acute pain or vestibular schwannoma, but less than COPD patients. Patients with long-term cure of Cushing's syndrome also believe that their illness is more cyclical than patients with acute pain. Patients with long-term remission of Cushing's syndrome report more negative consequences of the disease compared with patients with acute pain or vestibular schwannoma, but less negative consequences than patients with chronic pain. In addition, patients with long-term remission of Cushing's syndrome are less likely to seek medical care than patients with chronic pain. Moreover, patients with long-term cure of Cushing's syndrome have a lower perceived personal controllability of the disease compared with patients with acute pain, COPD, or vestibular schwannoma. Furthermore, patient with long-term cure of Cushing's syndrome have a lower perceived treatment controllability of the disease than patients with acute pain, but a higher perceived treatment controllability than patients with chronic pain or COPD. Finally, patients with long-term remission of Cushing's syndrome have a better personal understanding of their disease compared with patients with acute or chronic pain.

Patients' perceptions can be based on information from different sources. Therefore, patients' illness perceptions do not necessarily represent the medical status of the disease. This could explain why patients in remission of Cushing's syndrome perceive their illness as chronic or cyclical and believe that a psychological attribution might have caused Cushing's syndrome.

Patients with hydrocortisone dependency had stronger beliefs regarding the chronic nature and the cyclical nature of Cushing's syndrome than patients without hydrocortisone dependency. Furthermore, hypopituitarism was associated with the number of symptoms attributed to Cushing's syndrome, chronicity and fluctuations of the disease, and the perceived consequences of Cushing's syndrome. Therefore, hydrocortisone dependency and hypopituitarism both influ-

ence illness perceptions.

This study also demonstrates that there is a strong relationship between illness perceptions and QoL. Affected illness perceptions are correlated with a more impaired QoL. This has already been observed in multiple other medical conditions (24). This relationship is a relevant observation, since patients with long-term cure of Cushing's syndrome have persistent complaints reflected in impaired QoL (3-5). These complaints are often misunderstood and difficult to treat. Therefore, awareness of how these patients perceive their disease and its consequences could lead to better understanding of Cushing's syndrome and its long-term effects. Furthermore, the current data on persisting perceptions of a chronic, rather than of a cured disease in combination with altered coping strategies in these patients (6) permit the design of an intervention based on combinations of strategies including cognitive behavioral therapy, self-management training, and information on the negative effects of the disease. Self-management training involves exploring, eliciting, and changing illness perceptions of the patient, which in turn determines coping styles and self-management behavior (7;25). The intervention should be led by a health psychologist and endocrinologist and includes topics such as information about the illness and treatment, beliefs about consequences, beliefs about personal control, beliefs in self-efficacy, and the role of the social network (26). We speculate that with a targeted intervention, patients could be taught self-management skills and be better informed about the consequences of their disease. We believe that this approach might lead to improved QoL, since the present study shows that illness perceptions and QoL are strongly correlated. Similar self-management and educational interventions are currently available for patients with e.g. inflammatory bowel disease (27) and after stroke (28). Increasingly, partners of patients are involved in such self-management training, with encouraging results; the partners help in ensuring that the patient actually performs self-management skills in the home situation (26).

A possible limitation of this study might be the fact that the symptoms commonly occurring in Cushing's syndrome, which are described in the illness identity dimension, were not validated but instead based on the input of experienced endocrinologists. However, these symptoms were not used in the comparison of patients with Cushing's syndrome *versus* the patients from the reference samples and, therefore, do not influence the results of this study. A second limitation is the possibility that the difference in age distribution between the various groups might have affected the results. Nonetheless, in this study, age did not have an effect on illness perceptions. However, this does not necessarily control for the possibility of age as a confounder because of the relatively small sample size. Another possible limitation of this study is the use of convenience reference samples. Illness perceptions have never been studied in patients with endocrine diseases be-

fore, and therefore it was not straightforward to compare our patients to patients with other endocrine diseases. In the current explorative study, we decided to invite a large sample of patients with Cushing's syndrome and to compare them with existing available reference samples. Future studies examining the differences in illness perceptions between patients with various (endocrine) disorders in larger samples should include correction for possible confounders like age and gender.

In summary, there is strong correlation between illness perceptions and decreased QoL. Patients after long-term remission of Cushing's syndrome reported more negative illness perceptions compared with various reference samples. These results strongly point towards the need to develop, to apply and to evaluate a self-management and/or educational intervention aimed to improve these illness perceptions and thereby QoL in patients after remission of Cushing's syndrome.

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Chapter 3

Affected illness perceptions and the association with impaired quality of life in patients with long-term remission of acromegaly

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Abstract

Context and objective: Illness perceptions pertain to the beliefs patients develop about their illness, and these views are determinants of behavior directed at the illness. Illness perceptions are determinants of quality of life (QoL). QoL remains impaired in patients with biochemical control of acromegaly, but illness perceptions were never studied in these patients.

Aim: The aim of the current study was to explore illness perceptions and their association with QoL in patients with long-term biochemical control of acromegaly.

Design: This was a cross-sectional study.

Subjects: We included patients with long-term biochemical control of acromegaly (n=81), and compared them with Dutch reference populations: patients with acute pain (n=35) or chronic pain (n=63), Cushing's syndrome (n=52), chronic obstructive pulmonary disease (COPD; n=171), and vestibular schwannoma (n=80). Illness perceptions were evaluated using the Illness Perception Questionnaire-Revised, and QoL was assessed with the Physical Symptoms Checklist, EuroQoL-5D, and AcroQoL.

Results: Illness perceptions showed strong correlations with QoL. Patients after remission of acromegaly have a good understanding of their disease, but they experience a lack of personal control and are not likely to seek medical care compared with patients with acute disease (all $P<0.01$).

Conclusion: Illness perceptions of patients after long-term remission of acromegaly are affected and strongly related to QoL. Patients reported more negative illness perceptions than patients with acute illness, but more positive illness perceptions than patients with chronic diseases. Additional research is necessary to assess whether a self-management intervention might help in improving affected illness perceptions, and thereby improve QoL.

Introduction

Acromegaly is associated with typical signs and symptoms caused by excess of growth hormone (GH) and insulin-like growth factor 1 (IGF-1). Many of the systemic changes induced by previous excess of GH and/or IGF-I are not completely reversed upon successful biochemical treatment of active acromegaly (1). Impaired quality of life (QoL) persists despite long-term remission in acromegaly (2). Although decreased QoL may originate from persisting limitations due to irreversible effects of excessive GH and IGF-I exposure, an alternative hypothesis is that the psychological impact of suffering from this disease reduces QoL. This concept is supported by the observation that coping strategies are ineffective in patients with pituitary disease (3). Persistent, inappropriate thoughts about the disease and/or its treatment can influence general well-being. Moreover, patients and their doctors may have discrepant perceptions of the severity of the disease and the success of treatment. This concept can be studied by measuring illness perceptions.

Illness perceptions pertain to the way patients make sense of, and respond to, their illness and are conceptualized in the common sense model (CSM) of self-regulation. The CSM explains how patients generate both cognitive representations of, and emotional reactions to, their illness, integrating internal and external stimulus information with their pre-existing illness-theory (4). Leventhal *et al.* (5) designed the CSM, which starts from the premise that individuals are active problem solvers, who make sense of a threat to their health by developing a cognitive representation of the threat, which determines how the individual responds. Patients cluster these representations or ideas about the illness around five cognitive components: 1) identity: the label that is used by the individual to describe the condition and the associated symptoms, 2) cause: personal ideas about the cause of the condition, 3) time-line: expectations about the likely duration of the condition, 4) consequences: the physical, psychological, and social effects of the condition, 5) cure/control: the extent to which the condition is amenable to cure and/or control. These components form the illness representations, which determine the coping procedures of the patient (6). The sources of these perceptions are diverse. Therefore, these illness perceptions are subjective, may be partly or completely incorrect, and do not necessarily represent the actual medical status of the disease. At present, there are no studies that have evaluated illness perceptions in patients with acromegaly. Therefore, the aim of the study was to explore the illness perceptions of patients after long-term biochemical remission of acromegaly and compare these to reference groups from the literature.

Patients and Methods

Patients

We performed a clinical chart review of 156 patients with acromegaly. All were in biochemical remission at the time of the current study for at least 1yr. We invited these patients to participate in the current study. Seventy-five patients (48%) refused to participate for several reasons including old age, and/or debilitating disease. Eighty-one patients (52%) participated in the current study and completed the questionnaire on illness perceptions. Seventy-five patients also completed the QoL questionnaires.

The diagnosis of acromegaly had been established by clinical signs and symptoms and by biochemical tests, including insufficient suppression of GH during glucose tolerance test and increased IGF-1 levels for age. Biochemical control of acromegaly was defined by normal serum IGF-1 levels for age and serum GH levels below 1.9 μg/liter for all patients and, in patients without somatostatin analogue treatment, also by normal suppression of GH levels (<0.38 mcg/l) during glucose tolerance test (7). Remission was confirmed by repeating the tests 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 (20mg/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 70yr and only after at least 2yr of remission. Somatotrope insufficiency was treated with rhGH replacement, aiming at IGF-I concentrations in the normal range for age. Patients were treated with rhGH from 2005 onwards during a controlled trial of rhGH replacement (8). In addition, free T_4 and testosterone levels (in male patients) were assessed. If results were below the lower limit of the respective reference ranges, substitution with L- T_4 and/or testosterone was prescribed. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was provided.

Inclusion criteria for the current study were age over 18yr and remission defined by strict biochemical criteria for at least 1yr. The protocol was approved by the Medical Ethics Committee.

Protocol

Patients were asked to complete a questionnaire on illness perceptions and three questionnaires on QoL at home and return these in a prepaid envelope.

Illness Perception Questionnaire Revised (IPQ-R)

The IPQ-R was used to measure cognitive and emotional representations of acromegaly (9). This questionnaire was developed to assess the components of the illness representation of Leventhal's Self-Regulatory Model and is frequently used to study illness perceptions in chronic conditions (10-14). The IPQ-R is divided into three sections. The first part consists of the illness identity dimension, with a list of 14 commonly occurring symptoms and 11 symptoms commonly occurring in acromegaly. Patients are asked to rate whether or not they experienced the symptoms, and if they believe the symptom to be related to acromegaly (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 five-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), consequences (negative consequences of the disease), emotional representations (the likelihood to seek medical care), personal control (perceived personal controllability of the disease), treatment control (perceived treatment controllability of the disease), 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 entails causal attributions. This section consists of 18 statements concerning possible causes that patients consider that contributed to their disease, scored on a five-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 (9). A principal component analysis is a technique for identifying clusters/factors in a large set of variables. Once factors have been extracted, it is possible to calculate to what degree variables load onto these factors. Factor rotation can be used to calculate this and discriminate between factors. A varimax rotation is an orthogonal rotation that attempts to maximize the dispersion of factor loadings within factors. The rotation tries to load a smaller number of variables highly onto each factor, which in turn results in more interpretable clusters of factors (15). The analysis produced four factors accounting for 73% of the total variance. The first factor labeled psychological attributions accounted for 33% of the variance and consisted of the items stress or worries, family problems or worries, emotional state, mental attitude, own behavior, overwork, ageing, personality, altered immunity, and poor medical care. The second factor labeled risk factors accounted for 25% of the variance and consisted of the items

smoking, alcohol use, accident/injury, bacteria or virus, diet or eating habits, and pollution in environment. The third factor was labeled hereditary and accounted for 9% of the variance. This factor consisted of the item hereditary. The fourth factor labeled chance accounted for 6% of the variance and consisted of the item chance or bad luck. Because the third and fourth factor included only one item, no Cronbach's alpha could be calculated. Therefore, these last two factors were excluded from further analysis. Higher scores on the first and second causal subscales indicate stronger beliefs in those attributions in causing acromegaly.

Quality of life questionnaires

Physical Symptoms Checklist (PSC): This is a checklist of 55 physical symptoms that are mentioned in the DSM-III classification (16). The symptoms cover most organ systems. There are 11 general/ neurological items, 10 autonomic items, 8 musculoskeletal/pain items, 13 gastrointestinal items, 5 genital items and 4 items about feeling hot/cold. 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 (17).
EuroQoL-5D (EQ-5D): This QoL questionnaire measures five health dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores are expressed on a 1-3 scale per dimension, with a higher score indicating a 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 QoL state (18). On the VAS, a higher score indicates a better QoL.
AcroQoL: This is a disease specific QoL questionnaire designed to assess QoL in acromegaly (19). The AcroQoL consists of 22 questions on a five-point Likert scale. The response choices are divided into frequency of occurrence (ranging from 'always' to 'never') and degree of agreement with the items (ranging from 'completely agree' to 'completely disagree'). The total score ranges from 0-100, with a lower score indicating a greater impact on health-related QoL.
Six patients did not complete all QoL questionnaires.

Reference populations

We obtained reference values in patients with acute and chronic pain from the study that presented the revised version of the IPQ (9). The reference group with acute pain consisted of 35 subjects who were recruited from a private practice for physical therapy (20 men, 15 women, mean age of 36±12yr). These patients presented with a first-time peripheral painful injury that had been present for less than 6wk. The reference group of patients with chronic pain consisted of 63 sub-

jects (26 men and 37 women, with a mean age of 54±11yr) who were recruited from hospital-based chronic pain clinics. All patients experienced pain for longer than 3 months which was unexplained by medical signs alone. The reference group of patients treated for Cushing's syndrome was recruited from the Leiden University Medical Center outpatient clinic and consisted of 52 patients (7 men, 45 women, mean age of 54±11yr). Patients had been treated by transsphenoidal surgery, additional postoperative radiotherapy, or adrenal surgery. All patients were in remission with a mean duration of 16yr. Forty six patients (88%) had pituitary ACTH-dependent hypercortisolism, and six (12%) had Cushing's syndrome due to adrenal tumor. There were no significant differences between both groups of patients in the answers on the IIPQ-R (20). The fourth reference group consisted of 171 Dutch patients (112 men and 59 women, mean age 66±10yr) suffering from chronic obstructive pulmonary disease (COPD) (21). A chest physician had diagnosed all patients as suffering from emphysema and/or chronic bronchitis. We chose the reference sample of patients with COPD because COPD is a chronic illness and might therefore be comparable with respect to chronic complications of acromegaly after long-term remission. The fifth reference group consisted of 80 patients with vestibular schwannoma before treatment proposal and treatment (36 men, 43 women, and one anonymous responder). Mean age was 57yr (22). Thirty-eight percent of these patients suffered from an intracanalicular tumor. We included patients with vestibular schwannoma because these patients have to cope with the knowledge that there is a benign tumor present inside their head, which was also the case in patients with GH-secreting adenoma.

Because illness perceptions assess the perceptions of a specific disease, there are no norm values for the general population. Scores of patients with acute and chronic pain may be used instead (22).

Statistical analysis

Data were analyzed using PASW Statistics version 17.0.2 (SPSS Inc., Chicago, IL, USA). All data were presented as mean ± standard deviations, unless mentioned otherwise. Different treatment modalities of acromegaly were compared using an ANOVA with a *post hoc* analysis when appropriate, whereas patients with and without hypopituitarism were compared using a Student's t-test. The possible effect of duration of follow-up was explored by linear regression analysis. The standardized β coefficients of this analysis were reported. The level of significance for these analyses was set at $P \leq 0.05$. The primary analysis comprised the relationship between illness perceptions and QoL. Partial correlations were calculated controlling for duration of follow-up, and the level of significance was set at $P \leq 0.05$. The comparison of patients with a relatively better QoL and patients with a worse

QoL consisted of a Student's t-test with the level of significance set at P≤0.01, because of multiple comparisons.
Secondary analysis comprised the comparison of results in patients with long-term remission of acromegaly and of results in various reference groups. Means were calculated for all subscales of the IPQ and compared between groups using Student's t-test. Since multiple comparisons were used, the level of significance was set at P≤0.01.

Results

Sociodemographic and clinical characteristics

All 81 patients had long-term biochemical control of acromegaly, with a duration of follow-up of 16±10yr. Sixty-nine patients (85%) had been treated by transsphenoidal surgery and 19 patients (24%) by additional radiotherapy. Twenty-nine patients (36%) were treated with somatostatin analogues, 8 patients (10%) with pegvisomant, and 6 patients (7%) with dopamine agonists. Thirty patients (37%) were treated for some degree of pituitary insufficiency (Table 1). Figure 1 shows the self-reported symptoms of various organ systems. Most complaints involved musculoskeletal pain.

Table 1 Clinical characteristics

	Acomegaly, n=81
Gender (male/female)	47/34
Age (yrs)	60 (12)
Educational level (n)	Low: 23
	Medium: 26
	High: 32
Transsphenoidal surgery, n (%)	69 (85%)
Somatostatin analogue therapy, n (%)	29 (36%)
Pegvisomant therapy, n (%)	8 (10%)
Dopamine agonist therapy, n (%)	6 (7%)
Postoperative radiotherapy, n (%)	19 (24%)
Duration of follow-up (yrs)	16 ± 10
Hypopituitarism, n (%)	Any axis: 30 (37%)
	GH: 12 (15%)
	ACTH: 21 (26%)
	LH/FSH: 15 (19%)
	TSH: 21 (26%)
	ADH: 3 (4%)

Data are mean ± SD or number and %

Illness perceptions in acromegaly as measured with the IPQ-R

Illness identity dimension

Table 2 shows that 17-25% of the patients suffered from weight gain, sweating, back pain, snoring, and muscle pain, which they attributed solely to acromegaly. In addition, stiffness of the joints was one of the symptoms of the general illness identity dimension. This symptom was reported by 65% of the patients.

Scores of patients with long-term remission of acromegaly on various organ systems

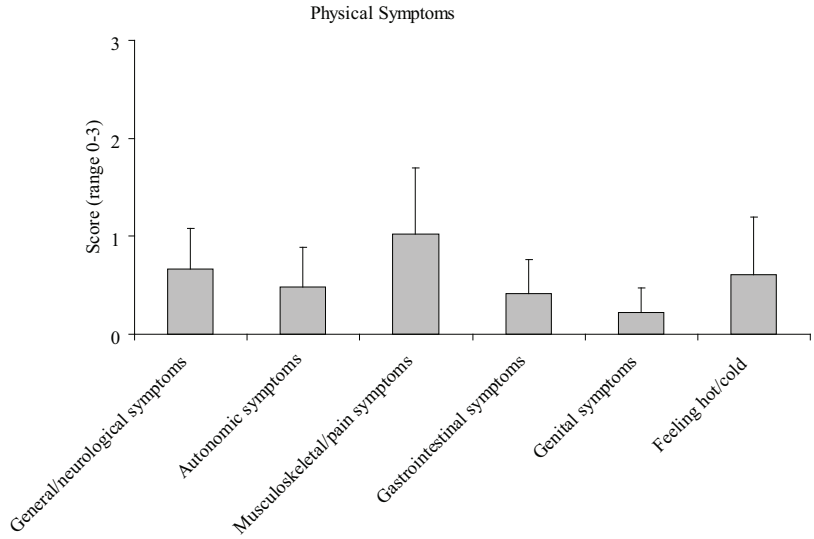

Figure 1. *Scores of patients after long-term remission of acromegaly on the various organ systems measured by the PSC. The minimal score on each scale is zero, whereas the maximum score is three.*

Causal attributions dimension

On the causal attributions dimension, patients during remission of acromegaly reported psychological attributions as the main perceived cause of acromegaly. Psychological attributions consist of stress or worries, family problems or worries, emotional state, mental attitude, own behavior, overwork, ageing, personality, altered immunity, and poor medical care as having caused acromegaly. Risk factors were also reported, but less frequently. The causal attribution risk factors consist of the items smoking, alcohol use, accident/injury, bacteria or virus, diet

Table 2 Symptoms related to acromegaly

Symptoms	Acromegaly, n=81
Gaining weight	21 (25%)
Sweating	19 (23%)
Back pain	18 (21%)
Snoring	17 (20%)
Muscle pain	17 (20%)
Hard time exercising	15 (18%)
Tingling hands	11 (13%)
Concentration problems	11 (13%)
Dental problems	11 (13%)
Memory impairment	8 (10%)
Abdomen complaints	5 (6%)

Data are n (%), symptoms commonly occurring in acromegaly of the 'illness identity' dimension of the IPQ-R

or eating habits, and pollution in environment.

Illness perception dimensions

We divided the patients in three treatment groups: 1) biochemical control by surgery, 2) biochemical control by surgery and radiotherapy and 3) biochemical control by primary or secondary medical treatment. Patients who received postoperative radiotherapy perceived more negative consequences (P=0.037) and had a worse personal understanding (P=0.041) compared with patients who had been cured by surgery alone. Additionally, patients with and without hypopituitarism were compared. Patients who were treated for some degree of pituitary insufficiency perceived less treatment control than patients who were free of pituitary insufficiency (P=0.034).

In a linear regression model, duration of follow-up was associated with perceived treatment control (β=-0.252, P=0.026) and personal understanding of the disease (β=-0.279, P=0.013).

Table 3 Quality of life in patients with acromegaly

	N=75
Physical Symptoms Checklist	
Total Score	27.6 (18)
EQ-5D	
Mobility	1.4 (1)
Self-care	1.0 (0)
Activity	1.5 (1)
Pain	1.8 (1)
Anxiety	1.4 (1)
VAS	69.4 (15)
AcroQoL	
Total Score	67.5 (15)

Data are mean (SD)

Relationship between illness perceptions and QoL

The scores of patients with acromegaly on the various QoL questionnaires are shown in Table 3. There were no significant differences in QoL between the three treatment groups. Levels of association between the IPQ-R dimensions and the QoL scales are shown in Table 4 as partial correlations, controlled for duration of follow-up.

There was a very consistent pattern of correlations between QoL and illness perceptions. A better QoL score was associated with better scores on the number of complaints attributed to acromegaly, perceived chronicity and fluctuations of acromegaly, perceived negative consequences, and the likelihood to seek medical

Table 4 Partial correlations between the IPQ-R dimensions and quality of life scales, controlling for duration of follow-up

	Physical Symptom Checklist	EQ-5D Mobility	EQ-5D Self-care	EQ-5D Activity	EQ-5D Pain	EQ-5D Anxiety	EQ-5D VAS	AcroQoL
Illness identity	.617 **	.410 **		.606 **	.462 **	.409 **	-.440 **	-.586 **
Timeline (acute/chronic)	.407 **						-.278 *	
Timeline (cyclical)	.380 **	.470 **		.356 **	.399 **		-.394 **	-.479 **
Consequences	.575 **	.405 **		.701 **	.586 **	.324 *	-.568 **	-.741 **
Emotional representations	.592 **	.392 **		.603 **	.670 **	.482 **	-.633 **	-.584 **
Personal control						-.273 *		.279 *
Treatment control	-.347 *	-.298 *		-.348 *		-.346 *		.334 *
Illness coherence	-.313 *	-.309 *				-.275 *		
Psychological attributions								
Risk factors								

Only correlations that reached statistical significance ($p<0.05$) are depicted, * $p<0.05$, ** $p<0.01$

care. A better QoL score was also associated with better scores on perceived personal and treatment control, and personal understanding of the disease.
Patients with low *versus* high scores on the various QoL questionnaires were compared, using the median value to define low versus high. Patients with high scores on the Physical Symptoms Checklist (indicating a more impaired QoL) attributed more symptoms to acromegaly (P<0.001), perceived more fluctuations (P<0.001), perceived more negative consequences (P=0.001), and were more likely to seek medical care (P<0.001) than patients with lower (and thus better) scores on this questionnaire. On the EQ-5D VAS, patients with a lower score (indicating a more impaired QoL) perceived more negative consequences (P<0.001), and were more likely to seek medical care (P<0.001) than patients with higher and better scores on the VAS scale. Patients with a lower score on the AcroQoL (indicating a more impaired acromegaly-specific QoL) attributed more symptoms to the acromegaly (P=0.001), perceived more negative consequences (P<0.001), and were more likely to seek medical care (P=0.001).

Illness perceptions in acromegaly compared with reference groups

Illness perceptions in patients after long-term cure of acromegaly compared with patients with acute or chronic pain

Compared with patients with acute pain, patients in remission of acromegaly perceived more chronicity (P<0.0001), more negative consequences (P=0.007), were less likely to seek medical care (P<0.0001), and perceived less personal control (P<0.0001), but had a better personal understanding of the disease (P<0.0001). Illness perceptions of patients with acromegaly were also compared with patients with chronic pain. Compared with those patients, patients with acromegaly were less likely to seek medical care (P<0.0001), but attributed less symptoms to their disease (P<0.0001), perceived less fluctuations (P<0.0001), perceived less negative consequences (P<0.0001), perceived more treatment control (P<0.0001), and had a better personal understanding of their disease (P<0.0001), see also Table 5 and Figure 2.

Illness perceptions in patients after long-term cure of acromegaly compared with patients treated for Cushing's syndrome

Compared with patients in long-term remission of Cushing's syndrome, patients with long-term biochemical control of acromegaly were less likely to seek medical care (P=0.001), but attributed less symptoms to their disease (P=0.007), perceived less fluctuations (P=0.01), and less negative consequences (P=0.0001), see also Table 5.

Table 5 Comparison of IPQ-R scores between acromegaly patients and other patient groups

IPQ-R	Acromegaly n=81	Acute pain n=35	Chronic pain n=63	Cushing's syndrome n=52	Chronic obstructive pulmonary disease n=171	Vestibular schwannoma n=80
Illness identity	**2.5 (2)**	2.8 (2)	6.2 (3)**	3.8 (3)*	5.6 (3)**	2.2 (2)
Timeline (acute/chronic)	**22.9 (6)**	13.4 (5)**	23.1 (4)	23.6 (7)	26.7 (4)**	20.6 (4)*
Timeline (cyclical)	**10.1 (4)**	9.4 (3)	12.9 (4)**	11.9 (4)*	12.1 (5)**	10.6 (4)
Consequences	**16.9 (5)**	14.2 (4)*	23.5 (4)**	20.4 (5)**	19.3 (6)*	16.4 (2)
Emotional representations	**12.6 (4)**	16.1 (4)**	19.8 (4)**	15.3 (5)*	14.1 (7)	15.3 (4)**
Personal control	**17.5 (5)**	22.9 (4)**	18.4 (4)	16.9 (6)	22.4 (6)**	19.1 (3)*
Treatment control	**18.1 (3)**	19.4 (3)	14.2 (3)**	16.7 (5)	14.3 (4)**	16.9 (3)
Illness coherence	**17.5 (3)**	9.3 (3)**	13.4 (5)**	17.0 (3)	NA	18.1 (4)
Psychological attributions *(score range 10-50)*	**18.2 (7)**	NA	NA	NA	NA	NA
Risk factors *(score range 6-30)*	**10.1 (4)**	NA	NA	NA	NA	NA

Data are mean (SD), * p<0.01 compared to patients with acromegaly, ** p<0.001 compared with patients with acromegaly, NA: not available or not attributable

Distribution of IPQ-R scores of patients with long-term remission of acromegaly, patients with acute pain, and patients with chronic pain

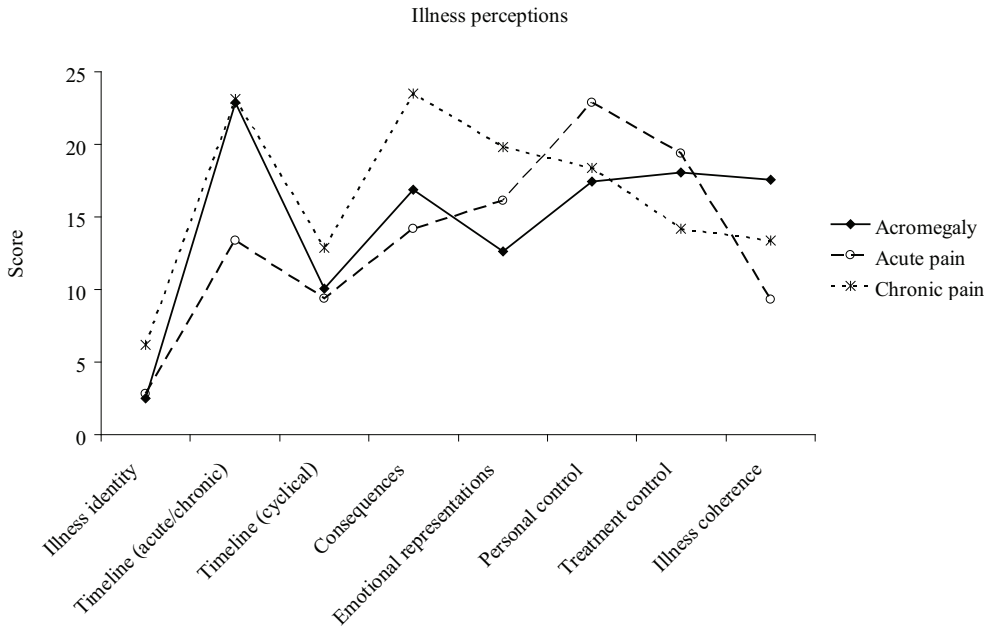

Figure 2. *Scores on the IPQ-R of patients after long-term remission of acromegaly, and patients with acute or chronic pain.*

Illness perceptions in patients after long-term cure of acromegaly compared with patients with COPD

The illness perceptions of patients in long-term remission of acromegaly were also compared with patients with COPD (Table 5). Patients with acromegaly perceived less personal control ($P<0.0001$), but attributed less symptoms to their disease ($P<0.0001$), perceived less chronicity ($P<0.0001$) and fluctuations ($P<0.001$), perceived less negative consequences ($P=0.0020$), and perceived more treatment control ($P<0.0001$).

Illness perceptions in patients after long-term cure of acromegaly compared with patients with vestibular schwannoma

Compared with patients suffering from a vestibular schwannoma, patients with acromegaly perceived more chronicity ($P=0.005$), were less likely to seek medical care ($P<0.0001$), and perceived less personal control ($P=0.006$), see also Table 5.

Discussion

This is the first study that describes illness perceptions in patients with acromegaly. In general, patients with long-term remission of acromegaly have a good understanding of their disease, but they experience a lack of personal control and are not very likely to seek medical care. Interestingly, there are clear differences between illness perceptions in acromegaly and other diseases. For example, acromegalic patients reported more negative illness perceptions than patients with acute pain or vestibular schwannoma, but more positive illness perceptions than patients with chronic conditions, like COPD. In addition, patients in long-term remission of acromegaly reported somewhat more positive illness perceptions than patients after long-term remission of Cushing's syndrome. Patients with long-term remission of acromegaly perceive impaired QoL. The illness perceptions in patients with acromegaly correlated strongly with QoL parameters, in accordance with observations in other conditions (23).

Treatment control and personal understanding of the disease were worse in patients after a longer duration of follow-up. We speculate that patients after longer duration of follow-up have less desire to have personal control over their acromegaly compared with patients with a shorter duration of follow-up. It might also be that longer follow-up of acromegaly indicated (at least for the patient) that acromegaly is a severe and chronic illness, which leads to less treatment control since patients feel the treatment they received did not cure acromegaly and also leads to less personal understanding since the doctors can not cure acromegaly and/or its (long-term) symptoms.

Illness perceptions in endocrine diseases have not been frequently studied. We documented some differences in illness perceptions between the various treatment groups of acromegalic patients. Moreover, there were also differences between patients with Cushing's syndrome and acromegaly. It is tempting to speculate that there are disease-specific characteristics in illness perceptions in addition to more general influences related to complaints or chronicity. Additional research is needed to see whether these findings can be extended to other endocrine diseases.

The reference groups all have their limitations since they differ considerably from acromegaly, but we believe that it is important to explore the illness perceptions of patients with acromegaly in reference to other illnesses since there are no data available on other hormonal illnesses. In addition, the essence of illness perception research is the perspective of the patient, independent of the medical objective of symptoms. A recent study by Figueiras and Alves (24) reported on perceptions of healthy people of serious illness with a new version of the IPQ-R for healthy people. With this questionnaire, the authors measured perceptions of

AIDS, tuberculosis, and skin cancer in a sample of 1113 healthy Portuguese subjects. The wording in the questionnaire was adapted for healthy individuals, i.e. 'this illness' instead of 'my illness'. AIDS, tuberculosis, and skin cancer are well-known illnesses and healthy individuals already have a common sense model of this illness, independent of the direct experience with this illness. However, acromegaly is a rare and not well-known disease. It is therefore not possible to ask a sample of healthy individuals about their illness perceptions concerning acromegaly without giving them information about the etiology, symptoms, and treatment of acromegaly beforehand. The provision of information about a rare and unknown disease would guide the illness perceptions in a certain direction, which in turn affects the reliability of the questionnaire. Therefore, we decided not to incorporate a group of healthy controls in the current study.

The illness perceptions of patients are based on various sources, which indicates that illness perceptions do not necessarily represent the actual medical status of the disease. This could explain, for example, why patients in long-term remission of acromegaly believe that a psychological attribution might have caused acromegaly. Psychological attribution consists of several causes i.e. stress or worries, family problems or worries, emotional state, mental attitude, own behavior, overwork, ageing, personality, altered immunity, and poor medical care. It is important for endocrinologists to explain to the patient what might have caused acromegaly, and ask the patient what their perceived cause of acromegaly is.

The current explorative study showed that there is a strong relationship between illness perceptions and QoL. More affected illness perceptions are correlated with more impaired QoL parameters. This has also been observed in patients after treatment for Cushing's syndrome (20) and in patients with various other diseases (23). This is a relevant observation, since patients with acromegaly suffer from impaired QoL even after long-term remission (2;25;26). The somatic and psychological factors that contribute to decreased QoL are not well-known, but most likely include musculoskeletal complaints (2), pituitary insufficiency (27;28) and the perception of the patients of their disease. A recent study (3) showed that patients with acromegaly use ineffective coping strategies. Additional research is necessary to establish whether, and to which extent, these illness perceptions and ineffective coping strategies can be improved which, in turn, might improve QoL.

A possible limitation of the present study is the fact that only 52% of the initially invited patients participated. We cannot exclude the possibility that the most distressed patients were more likely to participate, which might skew the results. However, this is an explorative study aiming to investigate illness perceptions in patients after long-term remission of acromegaly. We believe that the present results give a good first overview of how patients perceive acromegaly. Another limitation might be the fact that the reference samples differ in age distribution.

To date, it is unclear whether illness perceptions change with age. Although several determinants theoretically could contribute to our observations in these patients, a detailed analysis of each of these factors is not reliable considering the relatively small group of acromegaly patients. Future studies examining the differences in illness perceptions between patients with various (endocrine) disorders in larger samples should consider correcting for possible confounders like age.
In summary, in patients with long-term remission of acromegaly, illness perceptions are affected and correlate strongly with impaired QoL. Patients reported more negative illness perceptions than patients with acute illness, but more positive illness perceptions than patients with chronic diseases. We propose that a targeted self-management intervention might help in improving ineffective coping strategies and affected illness perceptions, and thereby improve QoL, at least in part, in patients with long-term remission of acromegaly.

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Chapter 4

Coping strategies in patients after treatment for functioning or non-functioning pituitary adenomas

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Abstract

Context and objective: Coping strategies may affect quality of life (QoL), which is decreased in patients after treatment for Cushing's disease, acromegaly, or non-functioning pituitary macroadenomas (NFMA). We aimed to explore coping strategies in these patients because this has never been done before.

Design: This was a cross-sectional study.

Subjects: We included patients treated for Cushing's disease (n=42), for acromegaly (n=80), and for NFMA (n=61). These patients were compared with three reference populations: an a-select sample from the Dutch population (n=712), patients with chronic pain (n=59), and patients receiving primary care psychology services (n=525). Furthermore, the three patient groups were compared with each other. Coping strategies were assessed by the Utrecht Coping List.

Results: Compared with the a-select sample, patients with pituitary adenomas reported less active coping (P<0.0001), sought less social support (P<0.0001), and reported more avoidant coping (P=0.008). In contrast, patients treated for pituitary adenomas reported somewhat better coping strategies than patients with chronic pain and those with psychological disease. When patients with different pituitary adenomas were compared, patients treated for Cushing's disease sought more social support than patients treated for NFMA (P=0.035).

Conclusions: Patients treated for pituitary adenomas display different and less effective coping strategies compared with healthy controls. A targeted intervention might help to stimulate patients to use a more active coping strategy and to seek social support, instead of an avoiding coping strategy. This might, in turn, improve their QoL.

Introduction

Pituitary adenomas may result in considerable, chronic comorbidity. Hormone overproduction results in classical syndromes like Cushing's disease and acromegaly. Mass effects of the tumor, especially in non-functioning pituitary macroadenoma (NFMA) result in visual field defects and hypopituitarism. Transsphenoidal surgery is an effective therapy for control of tumor mass and hormone overproduction in the majority of patients. If necessary, additional treatment with medical treatment or incidentally radiotherapy is available. Patients treated for Cushing's disease, acromegaly, and NFMA have persistently impaired quality of life (QoL) despite long-term cure (1-3). The factors causing reduced QoL in those patients with pituitary adenomas have not been fully elucidated.
Coping is the way in which someone reacts (behaviorally, cognitively, and emotionally) to situations that require adjustments in dealing with an adverse event and/or its consequences, for example an illness and its treatment (4). The common sense model (CSM) of illness cognition conceptualizes the processes involved in the adaption to threats imposed by illness. According to this CSM, coping strategies are determinants of medical outcomes (5). Furthermore, it is thought that coping may affect QoL (6).
At present, there are no studies that report coping strategies in patients with treated Cushing's disease, acromegaly or NFMA. Therefore, we aimed to examine the coping strategies of patients after treatment for pituitary adenomas in comparison with reference groups.

Patients and Methods

Design

We conducted a cross-sectional study in which patients treated for pituitary adenomas were invited to fill out a questionnaire on coping strategies.
Inclusion criteria were age over 18yr and treatment for pituitary adenoma at least 1yr ago. The protocol was approved by the institutional Medical Ethics Committee.

Patients

Patients with treated pituitary adenomas were invited to participate in the current study. These patients suffered from Cushing's disease, acromegaly, or NFMA. Patients were asked to complete a questionnaire on coping strategies at home and re-

turn this questionnaire in a prepaid envelope. Overall, the clinical characteristics of the non-participants did not differ from those of the participants.
Cushing's disease: A clinical chart review of 51 patients who had been treated by transsphenoidal surgery, if necessary followed by repeated surgery and/or post-operative radiotherapy was performed. We selected these patients based on their participation in an earlier study on psychopathology and personality traits (7). Nine patients (18%) refused to participate for several reasons including old age, and/or debilitating disease. Forty-two patients (82%) participated in the current study and completed the questionnaire.
Acromegaly: A clinical chart review of 156 patients who had been treated for acromegaly was performed. Fifty six patients (36%) refused to participate and an additional 20 patients (13%) did not (completely) fill out the measure used to assess coping (see below). Eighty patients (51%) participated in the current study and completed all questionnaires.
NFMA: A clinical chart review of 100 patients treated for NFMA was performed. Twenty five patients (25%) refused to participate and 14 patients (14%) did not (completely) fill out the measure used to assess coping (see below). Sixty one patients (61%) participated in the current study and completed all questionnaires.

Treatment and follow-up

Cushing's disease

Cushing's disease had been diagnosed based on internationally agreed guidelines, i.e. the clinical manifestations and positive biochemical tests including increased urinary excretion rates of free cortisol, decreased overnight suppression by dexamethasone (1mg) and, since 2004, elevated midnight salivary cortisol values, in addition to non-suppressed ACTH levels. All patients had been treated by transsphenoidal surgery, if necessary followed by repeated surgery and/or post-operative radiotherapy. Cure of Cushing's disease was defined by normal overnight suppression of plasma cortisol levels (<50nmol/l) after administration of dexamethasone (1mg) and normal 24h urinary excretion rates of cortisol (<220nmol/24h). Hydrocortisone independency was defined as a normal cortisol response to CRH or insulin-tolerance test (ITT). At the time of the current study, all patients were in remission of Cushing's disease.

Acromegaly

The diagnosis of acromegaly had been established by clinical signs and symptoms and by biochemical tests, including insufficient suppression of GH during glucose tolerance test and increased IGF-1 levels for age. Cure of acromegaly was defined by normal serum IGF-1 levels for age and serum GH levels below 1.9µg/l for all

patients and, in patients without somatostatin analogue treatment, also by normal suppression of GH levels (<0.38 mcg/l) during glucose tolerance test (8). Remission was confirmed by repeating the tests at yearly intervals. At the time of the current study, all patients were in remission or biochemically controlled. The biochemically controlled patients all had a IGF-I concentration in the normal range for age.

Non-functioning pituitary adenomas
After surgical treatment for NFMA, which was histopathologically confirmed, NFMA patients were included. Surgical treatment was performed in case of visual field defects in the majority of patients. Postoperatively, MRI scans were performed to detect tumor recurrence or regrowth. In case of progression, patients were referred for radiotherapy or an expectative management was chosen. At the time of the current study, all patients were free of recurrence of NFMA.

Follow-up
Patients were followed at our outpatient department. Patients were monitored for (recurrence of) disease, according to appropriate dynamic tests in patients with functioning adenoma and MRI scans in patients with non-functioning adenoma. In all patients, 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, confirmed by insulin-tolerance test or CRH test, the average dose of hydrocortisone was 20mg/d divided into 2 to 3 dosages. Evaluation of GH deficiency was performed by insulin-tolerance test and/or GHRH-arginine test, only in patients under the age of 70yr and only after at least 2yr of remission. Somatotrope insufficiency was treated with recombinant human GH replacement, aiming at a IGF-I concentration in the normal range for age. In acromegaly, patients were treated with GH from 2005 onwards during a controlled trial of recombinant human GH replacement (9). In addition, free T_4 and testosterone levels (in male patients) were assessed. If results were below the lower limit of the respective reference ranges, substitution with L- T_4 and/or testosterone was prescribed. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was provided.

Utrecht Coping List (UCL)
The UCL is an established Dutch coping scale with well-documented reliability and validity (10). Although its validity has not been tested for pituitary patients, the scores on the UCL in various medical samples have been reported in the international medical literature (6;11-13). The UCL consists of 47 statements where

the patients indicate whether they find these applicable to themselves. A four-point scale was used, ranging from seldom or never to very often. The statements lead to seven subscales: active coping (score ranging from 7-28), seeking distraction (score ranging from 8-32), avoiding (score ranging from 8-32), seeking social support (score ranging from 6-24), passive coping (score ranging from 7-28), expressing emotions (score ranging from 3-12), and fostering reassuring thoughts (score ranging from 5-20).

The subscale active coping refers to the ability to disentangle the situation and purposefully working to solve the problem. Seeking distraction refers to seeking distraction not to have to think regarding the problem and trying to feel better by smoking, drinking, or relaxation. Avoiding refers to leaving the problem for what it is or running away from it. Seeking social support refers to seeking social support for comfort and understanding or asking for help. Passive coping refers to being completely overwhelmed by the problem, a negative view and worrying about the past. Expressing emotions refers to the ability to show irritation or anger. Fostering reassuring thoughts refers to optimism (4).

Dutch population norms are available for nurses and women from the general population aged 18-65 years (4), as well as for chronic pain patients (10), and patients receiving primary care psychology services (14).

Reference populations

The a-select sample consisted of 712 women from two groups; the first group consisted of nurses with a mean age 30yr, while the second group was a random selection from the Dutch population with a mean age 47yr (4;14).

The chronic pain reference group consisted of 59 Dutch patients. This sample consists of 44 women and 15 men with a mean age of 64±6yr. Patients who reported pain in the hip or knee in the last month on three separate occasions during the study were classified as chronic pain patients.

The group of patients receiving primary care psychology services consisted of 525 Dutch patients who were in psychotherapy during the time of study. The group incorporated 329 women and 196 men, with a mean age of 37±12yr. Most patients were referred to a primary care psychologist by their general practitioner (37%) or self-referral (23%). All patients suffered from DSM-IV Axis-1 diagnosis, and an additional 68% also suffered from a DSM-IV Axis-2 personality disorder (14).

Statistical analysis

Data were analyzed using PASW Statistics version 17.0.2 (SPSS Inc., Chicago, IL, USA). All data were presented as mean ± standard deviations, unless mentioned otherwise. The primary analysis comprised the comparison of the results in pa-

tients who were treated for pituitary adenoma and of results in various reference groups. Means were calculated for all subscales of the UCL and compared between groups using Student's t-test. The level of significance for this analysis was set at $P \leq 0.01$, because multiple comparisons were performed. The secondary analysis comprised the comparison of results between patients treated for Cushing's disease, patients treated for acromegaly, and patients treated for NFMA. A general linear model was used to compare the UCL scores, with surgery, postoperative additional radiotherapy, and hypopituitarism as fixed factors. A *post hoc* analysis with a Bonferroni correction was performed in case of significant differences. The level of significance for this analysis was set at $P \leq 0.05$.

Results

Sociodemographic and clinical characteristics

Patients after treatment for Cushing's disease

Clinical characteristics of the patients are detailed in Table 1. All patients with Cushing's disease had been treated by transsphenoidal surgery, and nine patients (21%) had received additional radiotherapy because of persistent disease after surgery. At the time of the current study, all patients were in remission, with a mean duration of follow-up after cure of 13±10yr, and 27 patients (64%) were treated for some degree of pituitary insufficiency.

Patients after treatment of acromegaly

The clinical characteristics of patients after treatment for acromegaly are detailed in Table 1. Most of the patients (84%) had been treated by transsphenoidal surgery and 18 patients (23%) had been treated by additional radiotherapy because of persistent disease after surgery. Twenty eight patients (35%) were treated by somatostatin analogs, nine patients (10%) received pegvisomant therapy, and six patients (8%) received dopamine-agonist therapy. All patients were in remission or biochemically controlled at the time of study. The mean duration of follow-up was 16±10yr. At the time of the current study, 30 patients (38%) required treatment for pituitary insufficiency. Since not all patients were surgically cured, possible differences between surgically cured patients, patients receiving surgery and additional radiotherapy, and patients receiving chronic injections were analyzed using a one-way ANOVA with a *post hoc* Bonferroni correction. However, there were no significant differences in coping strategies between these groups.

Patients after treatment of NFMA

The clinical characteristics of patients after treatment for NFMA are detailed in Table 1. All patients had been treated by transsphenoidal surgery and 28 patients (46%) underwent additional radiotherapy because of persistent disease after surgery. At the time of the current study, all patients were free of recurrence of NFMA, with a mean duration of follow-up of 16±10yr, and all patients were treated for some degree of pituitary insufficiency.

Table 1 Clinical characteristics

	Cushing's disease (n=42)	Acromegaly (n=80)	NFMA (n=61)
Gender (male/female)	6/36	45/35	31/30
Age in years	54 (12)	60 (12)	63 (12)
Education (n)	Low: 19	Low: 23	Low: 12
	Medium: 11	Medium: 26	Medium: 24
	High: 12	High: 31	High: 25
Transsphenoidal surgery (%)	42 (100%)	67 (84%)	61 (100%)
Additional radiotherapy (%)	9 (21%)	18 (23%)	28 (46%)
Somatostatin analogue therapy, n (%)	NA	28 (35%)	NA
Pegvisomant therapy, n (%)	NA	9 (10%)	NA
Dopa agonist therapy, n (%)	NA	6 (8%)	NA
Duration of follow-up (yrs)	13 (10)	16 (10)	16 (10)
Hypopituitarism (%)	Any axis: 27 (64%)	Any axis: 30 (38%)	Any axis: 61 (100%)
	GH: 19 (45%)	GH: 12 (15%)	GH: 46 (75%)
	LH/FSH: 12 (29%)	LH/FSH: 15 (19%)	LH/FSH: 54 (89%)
	TSH: 17 (41%)	TSH: 21 (26%)	TSH: 46 (75%)
	ACTH: 24 (57%)	ACTH: 21 (26%)	ACTH: 47 (77%)

Data are mean (SD) unless otherwise stated; NA, not applicable

Coping strategies in patients after treatment for pituitary adenomas

Coping strategies in patients after treatment for pituitary adenomas compared with an a-select sample from the Dutch population

Patients treated for pituitary adenomas had significantly lower scores on active coping and seeking social support, and higher scores on the avoiding scale compared with an a-select sample from the Dutch population.

A lower score on active coping ($P<0.0001$) indicates that patients with pituitary adenomas performed worse when it came to disentangling the situation and purposefully working to solve the problem. A lower score on seeking social support ($P<0.0001$) suggests that patients with pituitary adenomas sought less comfort and understanding from others and therefore probably received less social support. The higher score on avoiding ($P=0.008$) indicates that they left the problem to what is was or ran away from it.

Figure 1 shows the scores of the patients with treated pituitary disease and the reference groups on the UCL, whereas Figure 2 shows how many patients scored in the most maladaptive percentile: 95th or higher percentile for avoiding and passive

Distribution of scores of patients treated pituitary adenomas and the reference groups

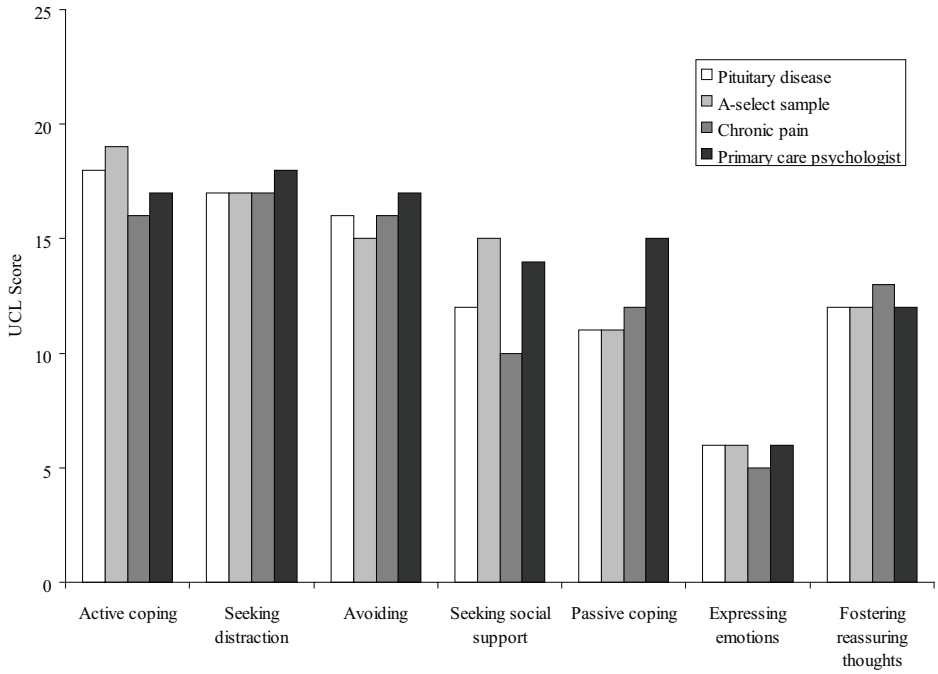

Figure 1: *Distribution of scores of patients with long-term cure of pituitary adenomas and the reference groups. Means are displayed in this figure. The coping strategies Avoiding and Passive coping are negative strategies, which means that a higher score indicates a more maladaptive coping strategy. The coping strategies Active coping, Seeking distraction, Seeking social support, Expressing emotions, and Fostering reassuring thoughts are positive strategies, which means that lower scores indicate a more maladaptive coping strategy.*

coping, and 5th or lower percentile for active coping, seeking distraction, seeking social support, expressing emotions, and fostering reassuring thoughts (4).

Coping strategies in patients after treatment for pituitary adenomas compared with other diseases

Coping strategies of patients with pituitary adenomas were compared with patients who suffered from chronic pain. The latter patient group reported pain in the hip or knee in the last month on three separate occasions. Compared with these patients, patients with treated pituitary adenomas scored higher on seeking social support ($P<0.0001$), indicating that patients with treated pituitary adenomas sought more comfort and understanding from others and therefore probably received more social support.

Coping strategies of patients with pituitary adenomas were also compared with the group of patients receiving primary care psychology services. All patients suffered

Distribution of UCL scores in the most maladaptive (<5th or >95th) percentile of patients with treated Cushing's disease, acromegaly, or NFMA

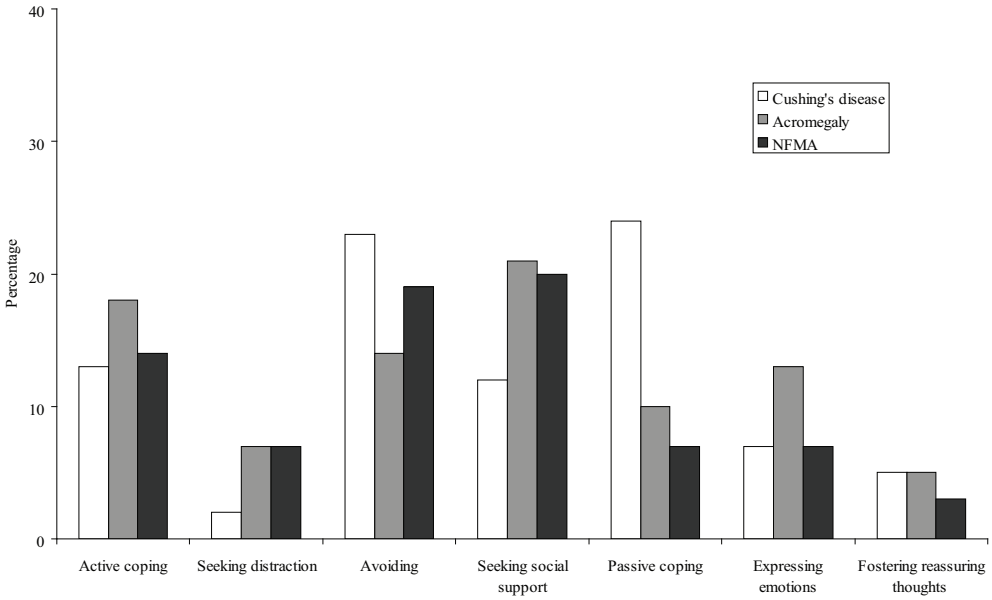

Figure 2: *Distribution of how many patients scored in the most maladaptive percentile based on the scores of an a-select sample from the Dutch population. ≥95th percentile for Avoiding and Passive coping, ≤5th percentile for Active coping, Seeking distraction, Seeking social support, Expressing emotions, and Fostering reassuring thoughts were used. Percentages are displayed in this figure.*

from a DSM-IV Axis-1 diagnosis, and an additional 68% also suffered from a DSM-IV Axis-2 personality disorder. Patients with pituitary adenomas scored lower on avoiding, seeking social support, passive coping, and expressing emotions.
A lower score on the coping strategy avoiding ($P<0.0001$) indicates that patients with pituitary adenomas were less intended to leave the problem to what it was. Lower scores on seeking social support ($P<0.0001$) suggest that patients with pituitary adenomas sought less comfort and understanding from others and therefore probably received less social support. Furthermore, a lower score on passive coping ($P<0.0001$) suggests that these patients were less overwhelmed by the problem. A lower score on expressing emotions ($P<0.0001$) suggests that patients with pituitary adenomas were less able to show irritation or anger compared with patients in primary care psychology services.
Patients with pituitary adenomas scored higher on active coping ($P=0.0005$) compared with patients receiving primary care psychology services, which indicates that patients with pituitary adenomas work better at disentangling the situation and purposefully working to solve the problem.

Table 2 Comparison of pituitary patients' UCL scores with other populations

UCL	Pituitary patients, n=183	A-select sample, n=712	Chronic Pain, n=59	Patients in primary care psychology services, n=525
Active coping	**17.6 (4)**	19 (5)**	16.4 (4)	16.5 (4)**
Seeking distraction	**17.1 (4)**	17 (6)	16.8 (4)	17.7 (4)
Avoiding	**15.9 (3)**	15 (6)*	16.0 (3)	17.1 (4)**
Seeking social support	**12.2 (4)**	15 (5)**	10.2 (3)**	13.5 (4)**
Passive coping	**11.0 (3)**	11 (5)	11.7 (4)	15.3 (4)**
Expressing emotions	**5.7 (2)**	6 (2)	5.3 (2)	6.3 (2)**
Fostering reassuring thoughts	**12.1 (3)**	12 (4)	13.3 (3)	11.6 (3)

Data are mean (SD), * p<0.01 compared with pituitary patients, ** p<0.001 compared with pituitary patients

Comparison of coping strategies in patients with Cushing's disease, acromegaly, and NFMA

Because sociodemographic characteristics do not influence coping strategies (14), we corrected only for surgery, additional radiotherapy, and hypopituitarism in comparing the patient groups. When the patient groups were compared, just one significant difference was found in coping strategies. When performing a *post hoc* analysis, patients with NFMA appeared to seek less social support compared with patients with Cushing's disease (P=0.035).

In addition, possible differences between short-term (<10yr) and long-term follow-up (≥10yr) in these pituitary patients were analyzed, correcting for diagnosis (i.e. Cushing's disease, acromegaly, or NFMA). In the short term follow-up group, there were 67 (27 males) patients (age 56±13yr) *versus* 116 (56 males) patients (age 61±12yr) in the long-term follow-up group. There was no significant difference in gender distribution. Age, however, differed between these two groups, with the long-term follow-up group being slightly older. Nonetheless, there were no significant differences in coping between these two groups. This suggests that the duration of follow-up does not influence coping strategies.

Furthermore, patients who had been treated by transsphenoidal surgery were compared with patients who had been treated by transsphenoidal surgery and additional radiotherapy, correcting for diagnosis (i.e. Cushing's disease, acromegaly, or NFMA). The group of patients who had been treated by surgery consisted of 116 subjects (52 males, age 58±13yr), and the group of patients receiving surgery and radiotherapy consisted of 54 subjects (23 males, age 63±12yr). Thirteen patients (all with acromegaly) were excluded from this comparison, since they had

not been treated by surgery. There were no significant differences in coping strategies between patients treated by surgery only and by both surgery and radiotherapy. This indicates that the addition of radiotherapy does not influence coping strategies in our cohort of patients.
Lastly, we also compared coping strategies between patients with hypopituitarism (i.e. insufficiency of at least one pituitary axis) and without hypopituitarism, correcting for diagnosis (i.e. Cushing's disease, acromegaly, or NFMA). There were 118 patients (52 males, age 58±13yr) with hypopituitarism and 65 patients (31 males, age 60±12yr) without hypopituitarism. There were no significant differences in coping strategies between these patient groups. This indicates that hypopituitarism also does not affect coping strategies.

Table 3 Comparison of pituitary patients

UCL	Cushing's disease (n=42)	Acromegaly (n=80)	NFMA (n=61)	P-value
Active coping	17.5 (3)	17.4 (4)	18.0 (3)	0.727
Seeking distraction	17.7 (3)	16.9 (4)	17.1 (4)	0.896
Avoiding	16.3 (3)	15.5 (4)	16.2 (3.1)	0.546
Seeking social support	13.3 (4)	12.1 (4)	11.4 (3)	0.016*
Passive coping	12.0 (3)	10.5 (3)	10.8 (3)	0.730
Expressing emotions	5.9 (2)	5.6 (2)	5.7 (2)	0.760
Fostering reassuring thoughts	12.3 (3)	12.1 (3)	12.1 (3)	0.664

Data are mean (SD), * Post Hoc Bonferroni analysis revealed a significant difference between Cushing's disease and NFMA (p=0.035)

Discussion

This explorative study demonstrates that patients after treatment for pituitary adenomas report less active coping and more avoidance coping and seek less social support compared with an a-select sample from the Dutch population. Compared with patients with chronic pain, patients treated for pituitary adenomas sought more social support. Patients after treatment for pituitary disease were also compared with patients in primary care psychology services. Patients with pituitary adenomas scored lower on avoiding, seeking social support, passive coping, and expressing emotions, but higher on active coping. This indicates that patients treated for pituitary adenomas report less effective coping strategies compared with the normal population, but apparently use more effective coping strategies than patients with chronic pain and patients in primary care psychology services. Furthermore, patients after treatment for Cushing's disease, acromegaly, and

NFMA did not differ from each other with respect to coping strategies, besides the fact that patients with Cushing's disease sought more social support than patients treated for NFMA. This is an interesting difference that might be due to more severe long-term effects of Cushing's disease compared with NFMA. Patients after long-term remission of Cushing's disease suffer from subtle cognitive impairments, increased prevalence of psychopathology and an increased incidence of maladaptive personality traits (7, 17). These impairments could be invalidating in everyday life, which in turn could lead to a higher need for social support.

This is the first study that explored coping strategies in patients treated for Cushing's disease, acromegaly, or NFMA. There are, however, two previous studies by one research group that reported coping strategies in small groups of patients (Cushing's disease n=18, acromegaly n=17) during or less than 1yr after treatment in a developing country (15;16). However, it is not clear whether patients report different coping strategies compared with controls and whether the coping strategies reported by the patients are negative or positive.

The present study explored coping strategies in patients treated for Cushing's disease, acromegaly, or NFMA. We believe this is valuable information, since these are chronic diseases with multiple invalidations after cure (1-3;7;17-21), which are often misunderstood and difficult to treat. Following successful treatment of hypercortisolism in Cushing's disease, signs and symptoms of the disease disappear. However, a large number of studies in humans and animal models have documented that prolonged, increased endogenous or exogenous exposure to glucocorticoids may have long-lasting adverse effects on behavior and cognition, due to functional and structural alterations in specific brain target areas (7;17;22;23). Furthermore, in acromegaly, many of the systemic changes induced by previous excess of GH and/or IGF-I are not completely reversed upon successful biochemical treatment of active acromegaly (20), which may also be true for the effects of GH and/or IGF-1 on the central nervous system (24). Patients after treatment for Cushing's disease, acromegaly, or NFMA suffer from persistently impaired QoL (1-3). Knowledge on coping strategies used by these patients is of importance, since this information can be used in designing an intervention based on, for example cognitive behavioural therapy, self-management training, and information on the negative effects of the disease. We speculate that, with a targeted intervention, patients could be taught self-management skills and be better informed about the consequences of their disease. We believe that this might lead to an improved QoL. Such self-management and educational interventions are already offered to, for example, patients with inflammatory bowel disease (24) and patients after stroke (25).

A possible limitation of this study might be the fact that the most distressed sub-

jects may be more likely participate, which is known as the concept of symptomatic volunteers. This should be kept in mind when interpreting the conclusions of this study. However, conversely, it might also be possible that patients who feel worse are less likely to participate. It is difficult to assess this issue in detail. Nonetheless, there we no differences in clinical characteristics between patients who participated and those who decided not to participate in the current study. In addition, the differences found between pituitary patients and the reference groups were very large and there is, at least in this cohort of patients, an obvious need for a self-management intervention.

In summary, patients treated for Cushing's disease, acromegaly, or NFMA display different and less effective coping strategies compared with healthy controls. Compared with patients with chronic pain and patients receiving primary care psychology services, patients treated for pituitary adenomas report somewhat better coping strategies. These results strongly point towards the need to develop, to apply and to evaluate coping skills training and self-management in patients with this condition.

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Chapter 5

Subtle cognitive impairments in patients with long-term cure of Cushing's disease

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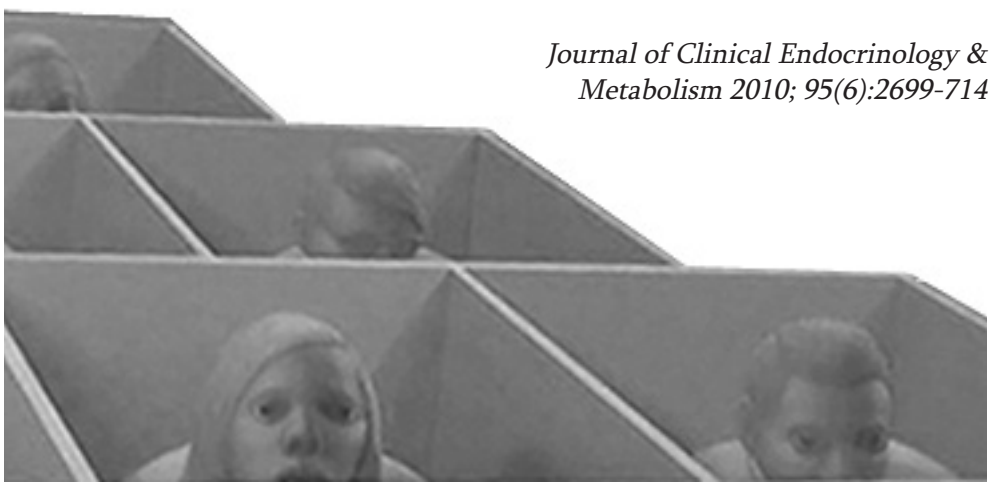

Abstract

Context and Objective: Active Cushing's disease is associated with cognitive impairments. We hypothesized that previous hypercortisolism in patients with Cushing's disease results in irreversible impairments in cognitive functioning. Therefore, our aim was to assess cognitive functioning after long-term cure of Cushing's disease.

Design: Cognitive assessment consisted of 11 tests, which evaluated global cognitive functioning, memory, and executive functioning.

Patients and Controls: We included 74 patients cured of Cushing's disease and 74 controls matched for age, gender, and education. Furthermore, we included 54 patients previously treated for nonfunctioning pituitary macroadenomas (NFMA) and 54 controls matched for age, gender, and education.

Results: Compared with NFMA patients, patients cured from Cushing's disease had lower scores on the Mini Mental State Examination (P=0.001), and on the memory quotient of the Wechsler Memory Scale (P=0.050). Furthermore, patients cured from Cushing's disease tended to recall fewer words on the imprinting (P=0.013), immediate recall (P=0.012), and delayed recall (P=0.003) trials of the Verbal Learning Test of Rey. On the Rey Complex Figure Test, patients cured from Cushing's disease had lower scores on both trials (P=0.002 and P= 0.007) compared with NFMA patients. Patients cured from Cushing's disease also made fewer correct substitutions on the Letter-Digit Substitution Test (P=0.039) and came up with fewer correct patterns on the Figure Fluency Test (P=0.003) compared with treated NFMA patients.

Conclusions: Cognitive function, reflecting memory and executive functions, is impaired in patients despite long-term cure of Cushing's disease. These observations indicate irreversible effects of previous hypercortisolism on cognitive function and, thus, on the central nervous system. These observations may also be of relevance for patients treated with high-dose exogenous glucocorticoids.

Introduction

Cushing's disease is characterized by excessive exposure to cortisol. Despite curative treatment, cardiovascular morbidity and mortality remain increased in these patients (1, 2). In addition, despite long-term cure of Cushing's disease, these patients have persistent physical and psychological complaints, associated with decreased quality of life parameters (3).

Patients with active Cushing's disease and Cushing's syndrome have cognitive impairments, especially in the memory domain. Previous studies reported impairments in memory, visual and spatial information, reasoning, verbal learning, and language performance (4 –10). Structures important in cognitive functioning, like the hippocampus and cerebral cortex, are rich in glucocorticoid receptors and are therefore particularly vulnerable to the glucocorticoid excess present in Cushing's disease (7). Starkman *et al.* (11) reported that 27% of the patients with active Cushing's syndrome fell outside the 95% confidence intervals for normal subject hippocampal formation volume and that hippocampal formation volume and performance on cognitive tests were positively related. In accordance, many other studies in humans and animal models have documented that prolonged, increased endogenous or exogenous exposure to glucocorticoids may have long-lasting adverse effects on behavioral, psychiatric, and cognitive functions, due to functional and, over time, structural alterations in specific brain target areas including the hippocampus (11–16). After treatment, all patients in the study by Starkman *et al.* (17) showed an increase in hippocampal formation volume, and half of the patients also showed an increase in cognitive function test scores. In contrast, other studies found no improvements in cognitive functioning within 1yr after treatment (18, 19). Some studies reported impaired cognitive functioning in patients with treated Cushing's disease (6, 18–20). However, these studies included only small numbers of subjects (n=35), and patients were tested relatively shortly (*i.e.* within the first 12–18 months) after cure of Cushing's disease. Therefore, it is presently unclear to which extent impairments in cognitive functioning remain present in patients with much longer duration of cure of Cushing's disease.

We hypothesized that previous hypercortisolism in patients with Cushing's disease results in irreversible impairments in cognitive functioning. Therefore, we evaluated cognitive functioning in patients after long-term cure for Cushing's disease and compared these data with those of age- and sex-matched controls as well as with those of patients treated for nonfunctioning pituitary macroadenomas (NFMA) and matched controls.

Subjects and Methods

Subjects

We included four groups of subjects: 1) patients cured from Cushing's disease and 2) gender-, age-, and education-matched control subjects and 3) patients previously treated for NFMA and 4) gender-, age-, and education-matched control subjects. The inclusion of these additional control groups was necessary because patients with Cushing's disease and NFMA differ with regard to age and gender.
We invited all patients in remission after treatment for Cushing's disease in our institution to participate (n=153). Each patient was asked to provide a control person of comparable age, gender, and education. Patients and their controls were evaluated at the same time. Patients who did not respond were encouraged by phone to participate. The response rate was 93%. Eighty-five patients were willing to participate, of whom 74 patients actually participated in all cognitive tests. Fifty-seven patients preferred not to participate, whereas 11 patients did not respond. The characteristics of patients who participated in the tests and those who did not participate were carefully compared. There were no differences in clinical characteristics between both groups. Reasons for not participating were distance to our institution, participation in other studies, old age, and debilitating disease.
The diagnosis of Cushing's disease had been established by clinical signs and symptoms and by biochemical tests including increased urinary excretion rates of free cortisol, decreased overnight suppression by dexamethasone (1mg) and, since 2004, elevated midnight salivary cortisol values in addition to suppressed ACTH levels. All patients were treated by Transsphenoidal surgery, if necessary followed by repeat surgery and/or radiotherapy. Cure of Cushing's disease was defined by normal overnight suppression of plasma cortisol levels (<100nmol/l) after administration of dexamethasone (1mg) and normal 24h urinary excretion rates of cortisol (<220nmol/24h). Hydrocortisone independency was defined as a normal cortisol response to CRH or insulin tolerance test. Patients were followed at our department with yearly intervals, and pituitary hormone substitution was prescribed in accordance with the results of yearly evaluation. Persistent cure of Cushing's disease was documented by normal values of a dexamethasone (1mg) suppression test, urinary cortisol excretion rates, and midnight salivary cortisol levels before participation in the current study.
In addition, we invited 132 patients with NFMA to participate in the study and to provide a control person (see above). The response rate was 94%. Fifty-four had undergone Transsphenoidal surgery and participated in all cognitive tests. There were no differences in clinical characteristics between participants and nonparticipants.
Pituitary function was assessed at yearly intervals. In patients who were gluco-

corticoid dependent after treatment, recovery of the pituitary-adrenal axis was tested twice a year. The dose of hydrocortisone was on average 20 mg/d divided into two to three dosages. After withdrawal of hydrocortisone replacement for 24h, a fasting morning blood sample was taken for the measurement of serum cortisol concentrations. Patients with serum cortisol concentration less than 120nmol/l were considered glucocorticoid dependent, and hydrocortisone treatment was restarted. Patients with serum cortisol levels of 120–500nmol/l were tested by ACTH stimulation tests (250μg). A normal response to ACTH stimulation was defined as a stimulated cortisol higher than 550nmol/l. In case the cortisol response to ACTH was normal the patients were tested by insulin tolerance test or CRH stimulation test. In case the cortisol responses to these tests were less than 550nmol/l, hydrocortisone treatment was restarted. Evaluation of GH deficiency was done by insulin tolerance test or arginine-GHRH test only in patients under the age of 70yr and only after at least 2yr of remission. Patients with an inadequate stimulation of GH by one of these tests were treated with recombinant human GH, aiming at IGF-I levels between 0 and +2 SD values. In addition, the twice-yearly evaluation consisted of measurement of free T_4 and testosterone (in male patients). If results were below the lower limit of the respective reference ranges, substitution with L-T_4 and/or testosterone was started. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was provided. Patient and treatment characteristics were collected from the patient records.

Twelve percent of the controls were treated for hypertension with appropriate blood pressure control (*i.e.* <140/90 mmHg) without evidence of hypertensive organ damage. Four percent of the controls were treated for type 2 diabetes mellitus with glycosylated hemoglobin levels less than 7% and without evidence of organ damage.

Inclusion criteria for the current study were age older than 18yr and remission defined by strict biochemical criteria at the time of study. Patients with present or previous drug or alcohol abuse or with neurological problems, not related to Cushing's disease or NFMA, were excluded. The protocol was approved by the Medical Ethics Committee, and written informed consent was obtained from all subjects.

Study design

A single study visit was planned, during which each subject of the two patient groups and the two control groups underwent anamnesis and performed the cognitive tests.

Cognitive evaluation

Eleven cognitive tests were to be completed to assess the full spectrum of cognitive functioning. A functional classification was used to subdivide the tests into the cognitive domains global cognitive functioning, memory, and executive functioning (21).

To measure global cognitive functioning, the Mini Mental State Examination (MMSE) was used. This is a 30-point questionnaire to assess cognition, with a higher score reflecting better performance (22). Memory was measured with the Wechsler Memory Scale, resulting in a memory quotient (MQ) based on scores in various subscales (23). The Verbal Learning Test of Rey, to measure verbal memory and learning, consists of three trials. Number of correctly recalled words was counted for each trial (24). The Rey Complex Figure, which measures drawing and visual memory, consists of two trials. A higher score indicates better visual memory (25).

Executive functioning was measured with the Trail Making Test (26), which measures psychomotor functioning and visuoconceptual tracking. Time used for both tests and number of mistakes were counted. The Stroop Color-Word Test (27) measures interference. Number of correct and wrong responses were counted. The Letter-Digit Substitution Test (28) measures mental flexibility and speed of information processing. Number of correctly substituted letters and errors within 60 sec were counted. The Digit-Deletion Test measures selective attention and concentration. Number of correctly deleted digits and the number of missed digits in 3 min were counted. The Figure Fluency Test measures the ability to produce new figures and assesses nonverbal mental flexibility and fluency (29). The number of correct figures, percentage of repeats, and percentage of wrong figures were counted. The FAS Test employs the letters F, A, and S and measures verbal mental flexibility and fluency (30). The number of correctly produced words and percentage of repeats and errors were counted. Furthermore, the Synonyms Subtest of the Groninger Intelligence Test-2 was used, with a higher score indicating better performance (31).

The Hospital Anxiety and Depression Scale (HADS) was used to measure anxiety and depression. The HADS consists of 14 items on a 4-point scale. Both anxiety and depression subscale scores range from 0–21 points. Higher scores indicate more severe anxiety and/or depression. A total score higher than 13 points on both subscales together is used to characterize subjects as anxious or depressed (32, 33).

Statistical analysis

Data were analyzed using SPSS for Windows version 16.0.2 (SPSS Inc., Chicago, IL, USA). All data are reported in tabular form, expressed as mean ± SD. The pri-

mary analysis comprised the comparison of the results between patients cured from Cushing's disease and their matched controls and between the patients with NFMA and their matched controls. Groups were compared using a general linear mixed model, with the matched patient-control couples as random factor. Secondary analysis comprised the comparison of results in relation to patient and treatment characteristics. To compare patients treated for Cushing's disease and for NFMA, mean and SD scores for each cognitive test were calculated for each control group, and subsequently, Z-scores were calculated for each patient group in relation to their appropriate control group. A general linear model was used to compare the Z-scores, with postoperative additional radiotherapy, hydrocortisone usage, and hypopituitarism as fixed factors. Independent variables affecting cognitive functioning in patients cured from Cushing's disease were explored by stepwise linear regression analysis. The standardized β-coefficients of this analysis were reported. To check the appropriateness of assumptions for each statistical analysis, we used Levene's test, Durbin-Watson test, histograms, and scatter plots. All assumptions were met, except for the independence assumption for parametric data. We therefore used nonparametric tests to analyze the clinical characteristics of patients *versus* controls (McNemar test, Friedman ANOVA, and Wilcoxon signed-ranks test). The level of significance was set at $P \leq 0.05$.

Results

Patient characteristics

Patients treated for Cushing's disease

All 74 patients were treated by transsphenoidal surgery, and 20 patients (27%) received additional radiotherapy because of persistent disease after surgery. The mean duration of remission was 13 ± 13 yr (range 1–51yr). The number of years in remission was calculated from the date of curative transsphenoidal surgery or, in case of persistent postoperative disease, from the date of the normalization of the biochemical tests after postoperative radiotherapy. Any degree of hypopituitarism was present in 43 patients (58%), and hydrocortisone replacement was given to 38 patients (51%). There were no differences between patients and controls with respect to age, gender, and education. We asked all patients whether they experienced limitations with respect to memory and/or executive functioning. Sixty-two percent reported memory problems, and 47% reported problems in executive functioning.

All patients with Cushing's disease also completed the HADS questionnaire. The mean scores for the depression subscale were 5.6±4.7 and for the anxiety subscale 5.0±4.7, resulting in total HADS scores of 10.5±8.8. This is well below the cutoff

Table 1 Clinical characteristics of patients cured from Cushing's disease and matched controls

	Cushing's disease (n=74)	Matched controls (n=74)	P-value
Gender (male/female)	13/61	13/61	1.00
Age (yrs)	52 ± 13	52 ± 13	0.26
Education (n)	Low (29) Average (19) High (26)	Low (28) Average (22) High (24)	0.28
Transsphnoidal surgery, n (%)	74 (100%)	NA	NA
Postoperative radiotherapy, n (%)	20 (27%)	NA	NA
Duration of remission (yr)	13 (13)	NA	NA
Duration of follow-up (yr)	16 (12)	NA	NA
Hypopituitarism, n (%)	Any axis: 43 (58%) GH: 26 (35%) LH/FSH: 19 (26%) TSH: 24 (32%) ADH: 11 (15%)	NA	NA
Hydrocortisone substitution, n(%)	38 (51%)	NA	NA

Data are mean ± SD, NA; not applicable

score of 13 (32, 33), which indicates that there is, on average, no clinical depression or anxiety in this cohort of Cushing's disease patients.

Patients treated for nonfunctioning pituitary macroadenomas

All patients (n=54) were treated by transsphenoidal surgery, and 24 patients (44%) received postoperative radiotherapy. Fifty patients (93%) required treatment for pituitary insufficiency, and hydrocortisone replacement therapy was given to 31 patients (57%). There were no differences between patients and controls with respect to age, gender, and education. Thirty-nine percent reported memory problems, and 24% reported problems in executive functioning.

Cognitive function

Patients with Cushing's disease versus matched controls

Patients with long-term cure of Cushing's disease did not perform worse on measures of global cognitive functioning. However, these patients showed a lower MQ on the Wechsler Memory Scale compared with controls (P=0.015), especially in the subtests concentration (P=0.023), visual memory (P=0.013), and associative learning (P=0.023). Furthermore, patients recalled fewer words than controls in the immediate and delayed recall trials of the Verbal Learning Test of Rey (P<0.001 on both trials). In accordance, patients scored lower than controls in the delayed trial of the Rey Complex Figure (P=0.040).

In tests assessing the executive functioning domain, the Letter-Digit Substitution Test showed that patients substituted fewer letters than controls (P=0.026). Fur-

Table 2 Clinical characteristics of the patients treated for NFMA and matched controls

	NFMA (n=54)	Matched controls (n=54)	P-value
Gender (male/female)	30/24	30/24	1.00
Age (yrs)	61± 11	59 ± 11	0.06
Education (n)	Low (18) Average (21) High (15)	Low (21) Average (15) High (18)	0.90
Operation, n (%)	54 (100%)	NA	NA
Postoperative radiotherapy, n (%)	24 (44 %)	NA	NA
Duration of follow up (yr)	15 (12)	NA	NA
Hypopituitarism, n (%)	Any axis: 50 (93%) GH: 40 (74%) LH/FSH: 32 (59%) TSH: 33 (61%) ADH: 6 (11%)	NA	NA
Hydrocortisone substitution, n(%)	31 (57%)	NA	NA

Data are mean ± SD, NA; not applicable

thermore, patients deleted fewer digits (P=0.035) on the Digit-Deletion Test and produced more repeated patterns on the Figure Fluency Test (P=0.045) when compared with controls.

When patients with short-term (<10 yr, mean 4±2 yr, range 1–8 yr) and long-term (≥10 yr, mean 24±11 yr, range 11–51yr) remission were compared, only a single test result was significantly different between these two groups. Patients with short-term remission had a higher percentage of errors on the FAS than those in the long-term remission group (3.1 *vs.* 0.9%, P=0.012).

Patients treated for NFMA vs. matched controls

Patients treated for NFMA did not perform worse on measures of global cognitive functioning. In tests assessing the memory domain, there were some differences between patients and controls. Patients scored lower on the subtest associative learning of the Wechsler Memory Scale (P=0.032) when compared with controls. In tests assessing executive functioning, there was a difference between patients and controls on the Trail Making Test. Patients needed more time on Trail A and B and made more errors on Trail A when compared with controls (P=0.001, P=0.035, and P=0.019, respectively). Furthermore, patients had a lower total score on the Stroop Color-Word Test (P=0.045).

When patients with short-term (<10 yr) and long-term (≥10 yr) duration of follow-up were compared, patients with long-term follow-up scored worse on the Groninger Intelligence Test (P=0.003) and made more errors on the first trail of the Trail Making Test (P< 0.001).

Table 3 Cognitive outcomes: patients cured from Cushing's disease *vs* matched controls

		Cushing's disease (n=74)	Matched Controls (n=74)	P-value
Global cognitive function				
MMSE	Score	27.9 (1.9)	28.3 (2.0)	0.173
Memory				
Wechsler Memory Scale	Memory Quotient	109.0 (16.8)	115.6 (15.6)	**0.015**
	Information	5.8 (0.4)	5.9 (0.4)	0.677
	Orientation	4.9 (0.2)	5.0 (0.2)	0.701
	Concentration	7.0 (2.0)	7.7 (1.4)	**0.023**
	Logical memory	6.3 (3.2)	7.1 (3.2)	0.118
	Digit span	9.9 (1.9)	10.3 (1.8)	0.231
	Visual memory	8.1 (3.0)	9.2 (3.4)	**0.013**
	Associative learning	16.0 (3.4)	17.2 (2.8)	**0.023**
Verbal Learning Test of Rey	Imprinting, total	5.8 (2.1)	6.3 (2.2)	0.154
	Immediate, total	9.4 (2.7)	11.0 (2.3)	**0.000**
	Delayed, total	7.5 (3.0)	9.4 (3.2)	**0.000**
Rey Complex Figure test	Immediate	17.2 (6.0)	18.9 (6.7)	0.063
	Delayed	16.7 (6.3)	18.6 (6.8)	**0.040**
Executive functioning				
Trail making test	Trail A, time	0.4 (0.3)	0.4 (0.4)	0.889
	Trail A, errors	0.1 (0.3)	0.2 (0.4)	0.111
	Trail B , time	1.3 (1.3)	1.2 (0.9)	0.415
	Trail B, errors	0.7 (1.7)	0.7 (2.2)	0.911
Stroop color-word test	Interference, total	39.8 (11.0)	42.0 (10.6)	0.220
	Interference, mistakes	0.3 (0.8)	0.2 (0.5)	0.297
Letter-digit substitution test	# correct	31.6 (8.0)	34.2 (7.9)	**0.026**
	# errors	0.1 (0.2)	0.1 (0.3)	0.555
Digit-deletion test	# correct	376.5 (102.2)	409.7 (91.3)	**0.035**
	# missed	5.0 (5.2)	4.3 (4.8)	0.385
Figure Fluency	# patterns	62.0 (23.4)	66.9 (22.7)	0.164
	% repeats	9.0 (11.3)	6.2 (5.7)	**0.045**
	% errors	17.2 (12.3)	16.9 (13.1)	0.866
FAS	# correct	33.1 (14.8)	36.2 (13.3)	0.168
	% repeats	1.8 (2.8)	1.2 (2.5)	0.131
	% errors	2.1 (3.8)	1.5 (4.8)	0.391
Synonyms subtest of the Groninger Intelligence test	Synonyms score	4.5 (1.9)	4.5 (1.8)	0.134

Data are mean (SD)

Table 4 Cognitive outcomes: patients cured from NFMA *vs* matched controls

		NFMA (n=54)	Matched ontrols (n=54)	P-value
Global cognitive function				
MMSE	Score	28.9 (1.1)	28.4 (1.4)	0.053
Memory				
Wechsler Memory Scale	Memory Quotient	118.2 (16.9)	118.1 (13.9)	0.965
	Information	5.9 (0.3)	5.9 (0.3)	0.693
	Orientation	4.9 (0.2)	5.0 (0.2)	0.651
	Concentration	7.6 (1.8)	7.3 (1.8)	0.526
	Logical memory	7.4 (3.3)	7.5 (2.6)	0.884
	Digit span	10.0 (1.6)	10.0 (1.9)	0.869
	Visual memory	8.9 (3.5)	8.6 (3.1)	0.618
	Associative learning	15.7 (3.0)	16.9 (2.6)	**0.032**
Verbal Learning Test of Rey	Imprinting, total	5.2 (1.9)	5.0 (1.9)	0.550
	Immediate, total	9.2 (2.9)	9.8 (2.2)	0.163
	Delayed, total	6.9 (3.4)	7.5 (2.7)	0.278
Rey Complex Figure test	Immediate	19.6 (6.6)	19.4 (5.8)	0.850
	Delayed	19.2 (6.4)	19.1 (5.8)	0.911
Executive functioning				
Trail making test	Trail A, time	0.6 (0.39)	0.4 (0.18)	**0.001**
	Trail A, errors	0.3 (0.5)	0.1 (0.3)	**0.019**
	Trail B , time	1.4 (0.69)	1.2 (0.6)	**0.035**
	Trail B, errors	0.5 (0.9)	0.4 (0.9)	0.724
Stroop color-word test	Interference, total	36.2 (9.1)	38.9 (8.8)	**0.045**
	Interference, mistakes	0.1 (0.4)	0.1 (0.4)	1.00
Letter-digit substitution test	# correct	31.2 (8.5)	32.7 (6.7)	0.230
	# errors	0.0 (0.2)	0.1 (0.4)	0.309
Digit-deletion test	# correct	366.3 (88.7)	389.2 (76.9)	0.148
	# missed	3.9 (4.3)	3.7 (4.1)	0.771
Figure Fluency	# patterns	47.9 (22.9)	53.0 (22.1)	0.597
	% repeats	9.2 (9.8)	8.5 (9.3)	0.840
	% errors	19.8 (11.4)	20.5 (16.3)	0.780
FAS	# correct	33.6 (13.4)	34.6 (11.7)	0.680
	% repeats	1.1 (2.0)	1.9 (2.6)	0.082
	% errors	2.3 (6.0)	2.2 (3.3)	0.919
Synonyms subtest of the Groninger Intelligence test	Synonyms score	5.0 (1.9)	5.0 (1.8)	0.958

Data are mean (SD)

Table 5 Cognitive function: comparison between patients with Cushing's disease and patients with NFMA by Z-scores, calculated for each patient group by comparison with their own matched control groups

		Z-scores Cushing's disease (n=74)	Z-scores NFMA (n=54)	P-value
Global				
MMSE	Score	-0.21 (-0.4 to 0.0)	0.34 (0.1-0.5)	**0.001**
Memory				
Wechsler Memory Scale	Memory Quotient	-0.42 (-0.7 to -0.2)	0.01 (-0.3 to 0.3)	**0.050**
	Information	-0.07 (-0.3 to 0.2)	0.07 (-0.2 to 0.4)	0.109
	Orientation	-0.07 (-0.3 to 0.2)	-0.10 (-0.4 to 0.2)	0.960
	Concentration	-0.47 (-0.8 to -0.1)	0.12 (-0.2 to 0.4)	**0.017**
	Logical memory	-0.26 (-0.5 to 0.0)	-0.03 (-0.4 to 0.3)	0.073
	Digit span	-0.21 (-0.5 to 0.1)	0.03 (-0.2 to 0.3)	0.230
	Visual memory	-0.31 (-0.5 to -0.1)	0.09 (-0.2 to 0.4)	**0.006**
	Associative learning	-0.41 (-0.7 to -0.1)	-0.43 (-0.7 to -0.1)	0.293
Verbal Learning Test of Rey	Imprinting, total	-0.23 (-0.5 to 0.0)	0.11 (-0.2 to 0.4)	**0.013**
	Immediate, total	-0.70 (-1.0 to -0.4)	-0.27 (-0.6 to 0.1)	**0.012**
	Delayed, total	-0.60 (-0.8 to -0.4)	-0.21 (-0.6 to 0.1)	**0.003**
Rey Complex Figure test	Immediate	-0.25 (-0.5 to 0.0)	0.03 (-0.3 to 0.3)	**0.002**
	Delayed	-0.27 (-0.5 to -0.1)	0.02 (-0.3 to 0.3)	**0.007**
Executive function				
Trail making test	Trail A, time	0.02 (-0.2 to 0.2)	1.16 (0.6-1.8)	0.081
	Trail A, errors	-0.21 (-0.4 to -0.1)	0.49 (0.1 to 0.9)	0.167
	Trail B , time	0.14 (-0.2 to 0.5)	0.36 (0.0-0.7)	0.939
	Trail B, errors	0.02 (-0.2 to 0.2)	0.06 (-0.2 to 0.3)	0.480
Stroop color-word test	Interference, total	-0.21 (-0.4 to 0.0)	-0.31 (-0.6 to 0.0)	0.823
	Interference, mistakes	0.21 (-0.1 to 0.6)	0.00 -0.3 to 0.2)	0.270
Letter-digit substitution test	# correct	-0.33 (-0.6 to -0.1)	-0.22 (-0.6 to 0.1)	**0.039**
	# errors	-0.08 (-0.3 to 0.1)	-0.15 (-0.3 to 0.0)	0.722
Digit-deletion test	# correct	-0.37 (-0.6 to -0.1)	-0.30 (-0.6 to 0.0)	0.359
	# missed	0.15 (-0.1 to 0.4)	0.05 (-0.2 to 0.3)	0.053
Figure Fluency	# patterns	-0.22 (-0.5 to 0.0)	-0.10 (-0.4 to 0.2)	**0.003**
	% repeats	0.49 (0.0-0.1)	0.04 (-0.2 to 0.3)	0.215
	% errors	0.03 (-0.2 to 0.2)	-0.04 (-0.2 to 0.2)	0.757
FAS	# correct	-0.24 (-0.5 to 0.0)	-0.09 (-0.4 to 0.2)	0.423
	% repeats	0.26 (-0.1 to 0.3)	0.03 (-0.5 to 0.5)	0.067
	% errors	0.13 (0.0 - 0.3)	0.03 (-0.5 to 0.5)	0.735
Synonyms subtest of the Groninger Intelligence test	Synonyms score	-0.24 (-0.5 to 0.0)	0.01 (-0.3 to 0.3)	0.215

Data are Z-scores mean (95% CI)

Comparison of Z-scores between patients cured from Cushing's disease and patients treated for nonfunctioning pituitary macroadenomas

Patients cured from Cushing's disease performed worse on the MMSE, which measures global cognitive functioning, compared with patients treated for NFMA (P=0.001). The observed difference between the two patient groups in the MMSE is most likely clinically not very relevant. Apparently, patients with long-term cure of Cushing's disease do not suffer from impaired global cognitive functioning, because there were no differences compared with their matched controls.

In the memory domain, patients cured from Cushing's disease had a lower MQ measured with the Wechsler Memory Scale compared with patients with NFMA (P=0.050) in the subscales concentration (P=0.017) and visual memory (P=0.006). On the Verbal Learning Test of Rey, patients cured from Cushing's disease recalled fewer words in the imprinting (P=0.013), the immediate recall (P=0.012), and the delayed recall trials (P=0.003) compared with NFMA patients. Furthermore, on the Rey Complex Figure, patients with cured Cushing's disease scored worse on both trials (P= 0.002 and P=0.007, respectively) when compared with NFMA patients.

In tests measuring executive function, patients cured from Cushing's disease made fewer correct substitutions on the Letter-Digit Substitution Test (P=0.039) and came up with fewer correct patterns on the Figure Fluency Test (P=0.003) compared with treated NFMA patients.

Factors associated with cognitive function in patients with Cushing's disease

As expected, age and educational level were associated with the outcomes of almost all cognitive tests, whereas gender was not. Potential factors of influence, including hypopituitarism, hydrocortisone dependency, duration of remission, and additional radiotherapy, were added in the stepwise linear regression model with adjustments for age and education. We calculated regression coefficients for test outcomes that were associated with duration of remission, which might indicate the potential for improvement.

Global cognitive functioning was not associated with any of the variables. In the memory domain, the Wechsler Memory Scale MQ was positively associated with duration of remission (β=0.276; P=0.017). In the executive function domain, the number of missed digits on the Digit-Deletion Test was positively associated with duration of remission (β=0.245; P=0.041) and additional radiotherapy (β=0.361; P=0.002). Furthermore, the number of correct patterns in the Figure Fluency Test was negatively associated with hypopituitarism (β=-0.278; P=0.012) and hydrocortisone dependency (β=-0.230; P=0.040). The percentage of mistakes in the Figure Fluency Test was positively associated with hydrocortisone dependency (β=0.224; P=0.048). The percentage of mistakes on the FAS Test was inversely as-

sociated with duration of remission (β=-0.254; P=0.034).
There was a significant correlation between the outcome on the Wechsler Memory Scale (MQ) and duration of remission (r=0.236; P=0.049). There was also a significant correlation between the number of missed digits on the Digit-Deletion Test and duration of remission (r=0.245; P=0.041), and the percentage of mistakes on the FAS and duration of remission (r=-0.254; P=0.034).

Discussion

This study demonstrates that cognitive function is impaired in patients despite long-term cure of Cushing's disease. These patients reported impairments in memory in daily life, which was confirmed by cognitive functioning tests. The performance was decreased in certain aspects of executive functioning and several memory tasks compared with matched controls. These impairments were not merely related to pituitary disease in general, because these patients with long-term cure of Cushing's disease also revealed impaired cognitive function compared with patients previously treated for NFMA. These observations indicate irreversible effects of previous hypercortisolism on cognitive function and, thus, on the central nervous system.
The outcomes of the cognitive tests are in general affected by many factors, including age, gender, and educational level. Because the controls and patients were perfectly matched, these potentially confounding factors did not influence our results or conclusions. We do not think that our results can be explained to a large extend by the difference in gender distribution between both patient groups. First, patients with long-term cure of Cushing's disease had impaired cognition compared with gender-matched controls. Second, we used Z-scores derived from the comparisons between patients and appropriately matched controls to compare the patients with cured Cushing's disease with patients treated for NFMA, because the gender differences were too large between these two patients groups to justify a direct comparison.
Several clinical characteristics influenced outcome parameters. Hypopituitarism was associated with mildly impaired executive functioning. Hydrocortisone dependency and additional radiotherapy were negatively associated with memory and executive functioning, whereas the duration of remission positively influenced memory and executive functioning. These findings do not invalidate our conclusions, because these factors were also present in patients treated for NFMA, who in general had better performances compared with the patients cured from Cushing's disease.
Table 6 summarizes all studies on the effect of Cushing's disease and syndrome on

cognitive functions, including the effects of treatment. Our observations extend those of previous studies. Four previous studies studied cognitive functioning in treated Cushing's disease patients, with a total of 98 patients and 77 controls. In the first study, patients with treated Cushing's disease (n=27) showed improvement of verbal fluency and recall within 18 months of follow-up, whereas brief attention did not change. This indicates that some but not all of the effects of previous glucocorticoid excess are reversible (20). The second study showed that there were no differences between patients (n=33) and matched controls in IQ during active disease and 12 months after treatment. There was, however, a positive relation for some subscales of the IQ test and recovery of the hypothalamic-pituitary-adrenal axis. There was also a negative association between some IQ subscales and duration of disease (18). The third study showed that 1yr after surgical treatment, high levels of cortisol caused long-lasting impairments in attention, visuospatial processing, memory, reasoning, and verbal fluency in patients with Cushing's syndrome (n=13) (19). Furthermore, the last study observed that patients with Cushing's disease (n=25) showed selective impairments in memory functions. After treatment, the eight patients who were retested showed amelioration of these memory impairments (6). Our study indicates that patients with long-term cure of Cushing's disease have impaired scores of memory and to a lesser extent in executive functions compared with both matched controls and treated NFMA patients. Our study differs in several respects from the previous studies. First, the number of patients included in our study was relatively large compared with the previous studies. Second, the duration of cure was very long in our study compared with previous studies. Third, we compared the patients with long-term cure of Cushing's disease both with matched controls and with patients previously operated for NFMA. From the studies summarized in Table 6, including our present study, the notion emerges that active Cushing's disease is associated with cognitive impairment and that treatment of Cushing's disease results in some but not complete recovery of cognitive impairment.

Several other studies evaluated the effects of pituitary adenomas, including ACTH-producing adenomas, on executive functioning and memory but did not specify the differences between different pituitary adenomas (34–36). Therefore, these studies do not permit any conclusion with respect to the specific effects of Cushing's disease compared with the effects of other pituitary adenomas on cognitive function.

Prolonged glucocorticoid excess modifies neurotransmitter function and neuronal structure of the central nervous system (7, 11). In rodents, chronic exposure to high levels of glucocorticoids impairs hippocampal long-term potentiation (12) and decreases hippocampal synaptic plasticity (13). In humans, endogenous active Cushing's disease is associated with cognitive impairment (6, 7, 20). The hip-

pocampus is one of the most sensitive structures in the brain for glucocorticoids and is crucial in cognitive function (37). The persistent impairments in cognitive function in patients with previous Cushing's disease might be explained by irreversible effects of previous glucocorticoid excess on the central nervous system, especially the hippocampus. Additional studies, including functional magnetic resonance imaging and postmortem analyses of the central nervous system, are required to evaluate the effects of previous glucocorticoid excess on brain areas of interest. Patients with long-term cure of Cushing's disease are a unique, monofactorial model to study the long-term effects of glucocorticoid exposure. The results of the current study may also apply to patients previously treated with high-dose glucocorticoids for nonendocrine diseases. In addition, the results might also be of relevance for patients with chronically increased glucocorticoid levels in conditions like depression (38, 39).

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 endpoints undertaken *vs.* an effect in one or more of those endpoints. 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 (40, 41), who advocate a restrictive approach toward adjustments for multiple comparisons. If we consider our own data and if we 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 Tables 3 and 4. Moreover, there are several arguments that cortisol excess can indeed cause irreversible effects on the central nervous system (see above). We designed this study in our patients cured from Cushing's disease 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 previous Cushing's disease documented in previous studies, although these had a different study design. According to Schulz and Grimes (40, 41), statistical adjustments somewhat rescue the positive results of scattershot analyses. However, we performed a targeted evaluation and analysis focused on cognitive function related to previous Cushing's disease 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 previous Cushing's disease and cognitive impairments.

A limitation of the present study was the cross-sectional study design. Conse-

quently, we do not have any information on premorbid functions, the effects of active Cushing's disease, and the extent of reversibility of the disturbed parameters. Nonetheless, these limitations do not invalidate our observations that patients with long-term cure have subtle impairments in cognitive function compared with matched controls and with patients treated similarly for NFMA. It might be argued that potential bias may have been introduced by the selection of the controls by the patients. In previous studies, we used similarly selected controls and compared the responses of these matched controls with those obtained from published Dutch control populations for several questionnaires (including HADS, Nottingham Health Profile, Multidimensional Fatigue Index, and Short Form) (3, 42, 43). In general, the conclusions obtained in the matched control subjects were in agreement with the literature-based reference data. In the present study, the self-selection of controls enabled a perfect match for an additional parameter, i.e. socioeconomic status, an important determinant of the outcomes of the questionnaires, in addition to age, gender, and education. Moreover, we used the same method of selection of controls for both groups of patients. Even though the selection procedure may have induced some, but unknown, bias, the data indicate that there were differences in outcome parameters between both groups of patients with the similar selection method of controls. Therefore, the outcomes are not a consequence of the study design or the selection procedure of the control subjects but, rather, of the long-term consequences of Cushing's disease.

In summary, there are subtle impairments in cognitive function in patients during long-term follow-up after cure of Cushing's disease compared with NFMA patients and matched controls. The greatest impairment was present in memory, although executive functioning was also affected. This impairment in cognitive function after treatment of Cushing's disease is not merely the result of pituitary disease in general and/or its treatment but includes specific elements most likely caused by the irreversible effects of previous glucocorticoid excess on the central nervous system.

Table 6 Overview of studies on cognitive function in patients with Cushing's disease

Author, year	Number of subjects	Gender (m/f)	Age yr (mean±SD)	Active/treated	Methods	Outcomes
Whelan, 1980 (4)	35 Cushing's syndrome	7/28	35±NA	Active	Michigan Neuropsychological Testbattery	13 patients had no signs of neuropsychological deficits, 10 patients had few and mild deficits, 8 had moderate and more frequent signs of impairment, and 4 had frequent and marked deficits. These impairments were more frequent and severe in nonverbal visual-ideational and visual memory functions.
Grattan-Smith, 1992 (34)	10 Cushing's syndrome 27 chromophobe A 15 prolactinoma 13 acromegaly 21 disfigured or disabled inpatients	NA	NA	Treated, duration of remission not given	Rey-Osterrieth complex figure, Controlled oral word association test, Trail making test, Wechsler memory scale, Warrington recognition memory test faces, New adult reading test	Not specified for Cushing's disease/syndrome. Overall, patients with pituitary adenomas experienced impairment of memory and executive function. This was not related to size or type of tumor, or the effects of treatment.
Starkman, 1992 (11)	12 Cushing's syndrome 1 normal subject	2/10	37±14	Treated, duration of remission not given	Magnetic resonance imaging, Wechsler memory scale-Russell modification, Trail making test	Hippocampal formation volume fell outside the 95% confidence interval for 27% of the patients. Furthermore, there was an association between reduced hippocampal formation volume and lower scores on verbal learning en memory tests.
Martignoni, 1992 (5)	24 Cushing's disease 24 matched controls	16/8	NA	Active disease, 7 patients were retested 6 months after treatment	Attention, memory, language, visuo-spatial, and logical abilities	Patients with active disease showed impairment in verbal and non-verbal episodic memory. The 7 re-tested patients showed a significant recovery of verbal memory.
Mauri, 1993 (6)	25 Cushing's disease 60 normal subjects (in patients)	8/17	36±14	Active, 8 patients were retested 6 months after treatment	Logic memory, Serial learning test, Digit span, Visual reproduction, Raven's colored progressive matrices, Digit symbol substitution test, Similarities, Cancellation task, Trail making test, Word fluency, Street's completion test	Patients with Cushing's disease showed selective impairment of memory functions. There were no deficits in other cognitive functions. The 8 retested patients showed significant amelioration of memory deficits.

Peace, 1997 (35)	36 pituitary tumor patients 36 controls	13/23	NA	27 treated (mean duration since surgery 9±6yr), 9 untreated	National adult reading test, Digit span, Auditory verbal learning test, Story recall, Recognition memory test for faces, Stroop neuropsychological screening test, Controlled oral word association test, Block design, Trail making test	Not specified for Cushing's disease/syndrome. Patients showed significant impairments in executive functioning and somewhat impairment in memory. Radiotherapy did not appear to be associated with cognitive functioning.
Peace, 1998 (36)	10 Cushing's disease 22 NFMA 21 prolactinoma 9 acromegaly 7 craniopharyngioma 23 healthy controls	NA	NA	Treated, duration of remission not given	National adult reading test, Digit span, Auditory verbal learning test of Rey, Story recall, Recognition memory test faces, Controlled oral word association, Block design, Trail making test	Not specified for Cushing's disease/syndrome. Surgically treated patients suffered from impairments in memory and executive functions. There were no significant negative effects associated with radiotherapy.
Forget, 2000 (7)	19 Cushing's disease 19 matched controls	18/1	47±11	Active	Visual target detection, Stroop test, Digit symbol substitution test, Trail making test, Judgement of line orientation, Bells test, Hooper visual organization, Gollin figures, Block design, Object assembly, Visual reproduction-copy, California verbal learning test, Logical memory, Digit span, Visual memory, Benton visual retention test, Comprehension, Picture completion, Picture arrangement, Arithmetic, Similarities, Raven's standard matrices, Vocabulary letter category fluency	Patients with Cushing's disease scored worse on all standardized neuropsychological tests, compared to their matched controls, particularly in processes involving selective attention and visual components. IQ scores of patients were within the normal range.
Dorn, 2000 (18)	33 Cushing's syndrome 17 matched controls	5/28	36±9	Active and twelve months post treatment	Wechsler adult intelligence scale-revised, profile of mood states, symptom checklist 90-revised	There were no group differences in cognitive function across time. There was, however, a trend for patients with Cuhsing's syndrome to have lower IQ scores at baseline. For some IQ subscales, there was a positive relation with recovery of the HPA axis and a negative association with duration of disease.
Starkman, 2001 (8)	48 Cushing's disease 38 healthy controls	11/37	37±14	Active	Wechsler adult intelligence scale-revised, Wechsler memory scale, semi structured clinical interview, Hammilton depression	Patients with Cushing's disease scored worse on 4 of the 5 verbal IQ subtests, and one nonverbal performance IQ subtest compared to controls. Verbal learning and delayed

					rating scale	recall were significantly decreased in patients.
Forget, 2002 (19)	13 Cushing's syndrome	2/11	47±13	One year after surgical treatment	See Forget, 2000 (7)	Compared to observations prior to treatment (Forget et al, 2000), there were no improvements in cognitive functioning in patients with Cushing's syndrome.
Starkman, 2003 (17)	24 Cushing's disease	4/20	34±13	Active and 16±9 months after surgery	Magnetic resonance imaging, Wechsler memory scale-Russell modification, Selective reminding test, Delayed memory (paragraphs and paired words), Vocabulary, Arithmetic, Symptoms checklist-90	All patients showed an increase in hippocampal formation volume after treatment and 18 patients showed an increase in caudate head volume. Fifty two - sixty one% of the patients showed an increase in learning score, while 61% of the patients showed an increase in memory score. For vocabulary, 25% had a better score, and 50% had an increased score for arithmetic.
Hook, 2007 (20)	27 Cushing's disease	4/23	39±13	Active, and after 3-5, 6-12, 13-18 months post treatment	Buschke selective reminding test, Digit span, Verbal fluency, Symptom checklist 90-revised, magnetic resonance imaging	Older and younger patients showed comparable levels of cognitive dysfunction before treatment. Younger patients showing a more rapid improvement. Verbal fluency and recall showed recovery, but brief attention did not. The improvement in verbal recall was associated with a decrease in cortisol levels and an increase in hippocampal formation volume one year after treatment.
Michaud, 2009 (9)	10 Cushing's syndrome 10 age-matched healthy controls 10 older controls	2/8	44±7	Active	See Forget, 2000 (7)	The age-matched control group performed better than the patients with Cushing's syndrome and older controls on 9 out of 23 tests. The older controls and patients performed similarly on these tests. This suggests that hypersecretion of glucocorticoids has aging-like effect on cognitive functioning in patients with Cushing's syndrome.
León-Carrión, 2009 (10)	15 Cushing's syndrome 15 healthy controls	0/15	39±14	Active	Simple letter cancelation test, Conditional letter cancelation test, Tower of Hanoi, Stroop test, Luria's memory words-revised	Patients showed significant attentional-dependent working memory deficits and impairment in delayed recall task. There were no differences between patients and controls on basic attentional and executive functioning.
Present study	74 Cushing's disease	13/61	52±13	13±13 yrs in	Mini mental state examination, Wechsler	Patients with long-term cure of Cushing's disease scored

74 matched controls 54 NFMA 54 matched controls	remission	memory scale, verbal learning test of Rey, Rey complex figure test, Trail making test, Stroop color-word test, Letter-digit substitution test, Digit-deletion test, Figure fluency, FAS, Groninger intelligence test synonyms subtest	significantly worse on tests measuring memory and to a lesser extend on tests measuring executive functioning compared to both matched controls and patients treated for NFMA. These observations indicate irreversible effects of previous hypercortisolism on cognitive function.

NA; not available, NFMA; non-functioning macro adenoma

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Chapter 6

Increased prevalence of psychopathology and maladaptive personality traits after long-term cure of Cushing's disease

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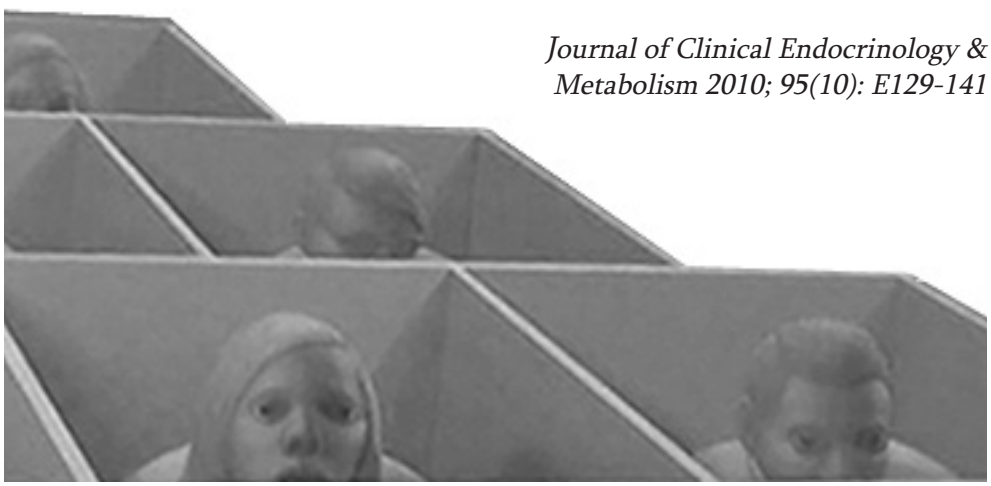

Abstract

Context and Objective: Psychopathology and maladaptive personality traits are often observed during the active phase of Cushing's disease (CD). We hypothesized that patients with long-term cure of CD show persistent psychopathology and maladaptive personality traits.

Design: Four questionnaires on frequently occurring psychopathology in somatic illnesses were used, including the Apathy Scale, Irritability Scale, Hospital Anxiety and Depression Scale, and Mood and Anxiety Symptoms Questionnaire short-form. Personality was assessed using the Dimensional Assessment of Personality Pathology short-form (DAPPs).

Patients and Controls: We included 51 patients cured of CD (16% men, 53±13 yr) and 51 matched controls. In addition, we included 55 patients treated for nonfunctioning pituitary macroadenomas (55% men, 62±10 yr), and 55 matched controls.

Results: Mean duration of remission was 11 yr (range 1–32yr). Compared with matched controls, patients cured from CD scored significantly worse on virtually all questionnaires. Compared with nonfunctioning pituitary macroadenoma patients, patients treated for CD scored worse on apathy ($P<0.001$), irritability ($P<0.001$), anxiety ($P<0.001$), negative affect and lack of positive affect ($P<0.001$ on both scales), somatic arousal ($P<0.001$), and 11 of 18 subscales of the Dimensional Assessment of Personality Pathology short-form ($P<0.05$).

Conclusions: Patients with long-term cured CD show an increased prevalence of psychopathology and maladaptive personality traits. These observations suggest irreversible effects of previous glucocorticoid excess on the central nervous system rather than an effect of pituitary tumors and/or their treatment in general. This may also be of relevance for patients treated with high doses of exogenous glucocorticoids.

Introduction

Patients with active Cushing's disease are exposed to excessive endogenous glucocorticoid levels, caused by ACTH-producingpituitaryadenomas.In these patients, psychopathology is often observed with major depression being the most common comorbid disorder, although mania and anxiety disorders have also been reported (1). After successful treatment of hypercortisolism, both physical and psychiatric signs and symptoms improve substantially (2, 3). However, these patients do not completely return to their premorbid level of functioning, and persistently impaired quality of life has been reported despite long-term cure (4). Furthermore, maladaptive personality traits were documentedafter treatment for Cushing's disease insome,but not all, studies (3, 5–7). Table 1 gives an overview of the current literature on psychopathology and personality traits in patients with Cushing's disease. Alarge number of studies in humans and animal models have documented that prolonged, increased endogenous or exogenous exposure to glucocorticoids may have longlasting adverse effects on behavioral and cognitive functions due to functional and, over time, structural alterations in specific brain target areas (8, 9). An important question is to what extent these adverse effects of glucocorticoids are reversible after withdrawal of glucocorticoid excess. At present, it is not clear whether, and to what extent, psychopathology and maladaptive personality traits persist after long-term cure of Cushing's disease. Therefore, our aim was to investigate psychopathology that is frequently present in patients with somatic illnesses and personality traits among long-term cured Cushing's disease patients, and compare them with matched controls. To exclude the possibility that pituitary adenomas and/or their treatment in general are associated with increased psychopathology or maladaptive personality traits, we also studied these parameters in patients previously treated for nonfunctioning pituitary macroadenomas (NFMA).

Table 1 Overview of studies on psychopathology and personality traits in patients with Cushing's disease

Author, year	Number of subjects	Gender (m/f)	Age yr (SD)	Active/treated	Methods	Outcomes
Cohen, 1980 (2)	29 Cushing's syndrome	7/22	42 (SD or range NA)	Almost all were seen during admission for diagnosis. A few were first seen immediately after surgery	Interviews. Detailed clinical history and an examination of mental state	Of all patients, 86% had distinct affective disorders. Twenty five patients suffered from depression, and one had manic and depressive episodes.
Starkman, 1981 (17)	35 Cushing's syndrome	7/28	35 (range 19-59)	Active	Semi-structured interview	Multiple psychiatric disturbances were found, including impairments in affect and vegetative functions. Low ACTH levels were associated with milder rather than pronounced depressed mood.
Haskett, 1985 (18)	30 Cushing's syndrome	6/24	37±11 (at time of diagnose)	6 untreated 24 treated (0-18 yrs before)	Schedule for affective disorders and schizophrenia-lifetime version of structured interview	83% of the patients met the criteria for an episode of affective disorder during the course of the disease. Patients frequently attempted to minimize or conceal psychiatric disturbance.
Starkman, 1986 (24)	23 Cushing's syndrome	5/18	37 (range 19-60)	Before and after treatment (2-72 months)	Semi-structured interview, Hamilton rating scale for depression	Depressed mood after treatment was significantly decreased in terms of decreased frequency compared to before treatment.
Sablowski, 1986 (6)	9 Cushing's disease 9 Acromegaly 6 Prolactinoma 24 Controls	NA	NA	Before and after surgery	Freiburger Personality Inventory, Gieβen test, State-trait-anxiety inventory	Pre-operative, there is a tendency to higher scores of trait-anxiety in pituitary patients compared to controls. This did not change after surgery. Furthermore, Cushing's disease patients seemed more nervous and restrained than acromegaly patients.
Loosen, 1992 (19)	20 Cushing's disease 20 major depressive disorder	1/19	39±11	Active	Structured clinical interview for DSM-III-R, Research diagnostic criteria, Family history research diagnostic criteria	79% of the patients received the diagnosis generalized anxiety disorder, 68% major depressive disorder, and 53% panic disorder.
Kelly, 1996 (20)	209 Cushing;s	47/162	39 (range 8-74)	Active	Clinical interview, Present	When Cushing's syndrome was diagnosed, 57% of

	syndrome 24 pituitary adenoma patients				State Examination, Hamilton rating scale for depression	the patients showed significant psychiatric illness, usually depression.
Kelly, 1996 (3)	43 Cushing's syndrome 24 acromegaly and prolactinoma	10/33	NA	Before and after treatment	Present state examination, Hamilton rating scale Crown-Crisp experiential index, Eysenck personality inventory	Present state examination: only 19% of the active Cushing's syndrome patients were normal, whereas 87% of the controls were normal. Depression and all scales of the Crown-Crisp improved after treatment. When patients were re-assessed after appropriate treatment, there was a significant decrease in neuroticism score but no change in extraversion.
Dorn, 1995 (21)	33 Cushing's syndrome 17 Matched hospitalized controls	5/28	36±9	Hypercortisolaemic during interview	Interviews, Atypical depression diagnostic scale, Hamilton rating scale, self-report instruments, medical records information	Anytime during the active phase, 67% of the patients had at least one diagnosis. Atypical depression was the most frequent finding (52%). The duration of CS was an important factor in predicting whether patients sought psychological intervention.
Dorn, 1997 (22)	33 Cushing's syndrome	5/28	36±9	Before and 3, 6, en 12 months after correction for hypercortisolism	Interviews, Atypical depression diagnostic scale, Hamilton rating scale, self-report instruments, medical records information	Before cure, 67% had significant psychopathology. After cure, overall psychopathology decreased to 54% at 3 months, 36% at 6 months, and 24% at 12 months. There was an inverse correlation between psychological recovery and baseline morning cortisol. Atypical depression remained the most frequent finding.
Sonino, 1998 (23)	162 Cushing's disease	38/124	38±13	Active	Paykel's clinical interview for depression	54% of the patients suffered from a major depressive disorder during the course of their illness. Depression was associated with older age, female sex, higher pretreatment urinary cortisol levels among others.
Flitsch, 2000 (29)	19 Cushing's disease 18 Acromegaly 11 NFMA	7/12	34±12	Before and after (6 months) transsphenoidal microsurgery	Semi-structured interview, Reiburger Personlichkeitsinventar, State-trait-anxiety-inventory, Rosenzweig	Most common psychopathological signs were excitability and depression. At least one of these signs was found in 12 out of 19 Cushing's disease patients. Six-eight months after surgery, majority of the

					picture frustration test, Befindlichkeitsskala, Giessener Beschwerdebogen	Cushing's disease patients (10 of 19) noticed an increase in physical well-being.
Sonino, 2006 (7)	24 Cushing's syndrome 24 Healthy matched controls	5/19	35±11	1-3 yrs in remission	Tridimensional personality questionnaire, Symptom rating test	No significant differences in personality dimensions between patients and controls. On the Symptom rating test, patients scored higher on anxiety, depression and psychotic symptoms compared to controls.
Sonino, 2007 (25)	Cushing's disease: 15 Other pituitary: 71 Non-pituitary: 60	uk	39 ± 12 (total sample)	Cured disease or in remission for >9 months <3 years	Structured clinical interview for DSM-IV, Diagnostic criteria for psychosomatic research, Psychosocial index, Medical outcomes study	Patients with Cushing's disease reported more stress and less well-being than controls. Twenty percent of the patients suffered from major depression, 33% from generalized anxiety disorder, and 47% of irritable mood.
Present study	67 Cushing's disease 67 Matched controls 55 NFMA 55 Matched controls	10/57	Cushing's disease: 53 (13) NFMA: 62 (10)	13±13 yrs in remission	Apathy Scale, Irritability Scale, Hospital Anxiety and Depression Scale (HADS), Mood and Anxiety Symptoms Questionnaire short-form (MASQ), and Dimensional Assessment of Personality Pathology short-form (DAPP)	Patients with cured Cushing's disease have an increased prevalence of psychopathology and maladaptive personality traits compared to matched controls and patients treated for NFMA. Compared to NFMA patients, the patients treated for Cushing's disease scored worse on apathy, irritability, negative affect and lack of positive affect, somatic arousal, and eleven out of eighteen maladaptive personality traits of the DAPP.

NA; not available, NFMA; non-functioning macro adenoma

Patients and Methods

Patients

We included four groups of subjects: 1) patients with long-term cure of Cushing's disease, and 2) gender-, age-, and education level-matched control subjects for these patients with previous Cushing's disease, 3) patients previously treated for NFMA, and 4) age-, gender-, and education level-matched control subjects for these patients previously treated for NFMA. The inclusion of these two separate control groups was necessary because patients with Cushing's disease and NFMA patients differ considerably with respect to age and gender distribution. We performed a clinical chart review of 85 patients who had been treated by transsphenoidal surgery if necessary followed by repeated surgery and/or postoperative radiotherapy. All were in remission of Cushing's disease at the time of the current study for at least 1yr. The long-term treatment outcome of these patients has been characterized and described in detail (10). We invited these patients to participate in the current study. Each patient was asked to provide a control person of comparable gender, age, and education level. Gender and education had to be the same, and age was allowed to differ maximally by 10 yr. Patients who did not respond were encouraged by phone to participate. Thirty-four patients (40%) refused to participate for several reasons including living outside The Netherlands, which implicated that the patients were not able to use the prepaid answer envelope to return the questionnaires. The other reasons were old age and/or debilitating disease. Fifty-one patients (60%) participated in the current study and completed all questionnaires. The clinical characteristics of the nonparticipants did not differ from those of the participants.

Cushing's disease had been diagnosed based on the clinical manifestations and positive biochemical tests including increased urinary excretion rates of free cortisol; decreased overnight suppression by dexamethasone (1mg); and, since 2004, elevated midnight salivary cortisol values in addition to non-suppressed ACTH levels. All patients had been treated by transsphenoidal surgery, if necessary, followed by repeated surgery and/or postoperative radiotherapy. Cure of Cushing's disease was defined by normal overnight suppression of plasma cortisol levels (<50nmol/l) after administration of dexamethasone (1mg) and normal 24h urinary excretion rates of cortisol (<220nmol/24h). Hydrocortisone independency was defined as a normal cortisol response to CRH or insulin-tolerance test (ITT). In addition, we invited 132 patients with NFMA treated previously by transsphenoidal surgery to participate in the study. The response rate was 94%. Fifty-five patients (42%) completed all questionnaires. There were no differences in clinical characteristics between participants and nonparticipants. Each patient was asked to provide a control person of comparable gender, age, and education level.

Pituitary function was assessed at yearly intervals in both patient groups. In patients cured of Cushing's disease who were glucocorticoid dependent after treatment, recovery of the pituitary-adrenal axis was tested twice a year. The dose of hydrocortisone was on average 20 mg/d divided into two to three dosages. After withdrawal of hydrocortisone replacement for 24h, a fasting morning blood sample was taken for the measurement of serum cortisol concentrations. Patients with serum cortisol concentration less than 120 nmol/l (blood samples obtained between 0800 and 0900 h) were considered to be glucocorticoid dependent, and hydrocortisone treatment was restarted. Patients with serum cortisol levels between 120 and 500 nmol/l were tested by ITT or CRH stimulation. In case the cortisol responses to these tests were less than 550 nmol/l, hydrocortisone treatment was restarted. In patients under the age of 70yr, GH-deficiency was assessed by ITT or combined GHRH-arginine test, after at least 2yr of remission of Cushing's disease. Patients with inadequate stimulation of GH by one of these tests were treated with recombinant human GH, aiming at IGF-I levels between 0 and +2 SD values. In addition, free T_4 and testosterone levels (in male patients) were assessed. If results were below the lower limit of the respective reference ranges, substitution with L-T_4 and/or testosterone was prescribed. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was provided.
Inclusion criteria for the current study were age older than 18yr and remission defined by strict biochemical criteria for at least 1yr. Patients with present or previous drug or alcohol abuse or with neurological disorders not related to Cushing's disease or NFMA were excluded. The protocol was approved by the Medical Ethics Committee and written informed consent was obtained from all subjects.

Questionnaires

Patients and controls were asked to complete questionnaires on psychopathology and personality at home and to return them in a prepaid envelope.

Apathy scale

Apathy was assessed using the Apathy Scale, which was designed at the Johns Hopkins School of Medicine (Baltimore, MD). The Apathy Scale consists of 14 questions on a four-point scale measuring the different features of apathy in the 2 wk before. The score for each item ranges from 0 (no apathetic behavior) to 3 (maximum intensity of apathetic behavior). The total score ranges 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 (11, 12).

Irritability scale
Irritability was assessed using the irritability scale that consists of 14 items on a four-point scale measuring different features of irritability in the 2 previous weeks. The total score ranges from 0 to 42 points, with higher scores indicating greater irritability. A total score of 14 points or more is being used to characterize subjects as irritable (12).

Hospital Anxiety and Depression Scale (HADS)
Anxiety and depression were assessed using the HADS that consists of 14 items on a four-point scale. Both anxiety and depression subscale scores range from 0 to 21 points. Higher scores indicate more severe anxiety and/or depression. A score greater than 8 points on one of the subscales is being used to characterize subjects as being anxious or depressed respectively (13, 14).

Mood and Anxiety SymptomsQuestionnaire shortform (MASQ-30)
The MASQ-30 consists of 30 items assessing symptoms that occur in mood and anxiety disorders subdivided into the three subscales of negative affect, lack of positive affect, and somatic arousal. The scores for each subscale ranges from 10 to 50, with higher scores indicating more severe negative affect, more lack of positive affect, or more somatic arousal. There are no formal cutoff scores (15).

Dimensional Assessment of Personality Pathology short-form (DAPPs)
The 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 a maxima of 30–40 and higher scores indicating more pronounced maladaptive personality traits. There are no formal cut-off scores (16).

Statistical analysis

Data were analyzed using PASW Statistics version 17.0.2 (SPSS Inc., Chicago, IL, USA). All data were presented as mean ± SD, unless mentioned otherwise. When data were missing, multiple imputation was used to impute the missing values. In the present study, this was not a major issue because only approximately 0.5% of the data were missing and therefore imputed. Ten different imputations were calculated and the pooled descriptives and P-values were used. The primary analysis comprised the comparison of the results between patients cured of Cushing's disease and their matched controls and between the patients with NFMA and their matched controls. Groups were compared using an independent-samples *t*

test. A χ^2 test was used in case of categorical data. Secondary analysis comprised the comparison of results of patients treated for Cushing's disease and patients treated for NFMA. Mean and SD scores for each questionnaire subscale were calculated for each control group, and subsequently Z-scores were calculated for each patient group in relation to their appropriate control group. Independent variables affecting psychopathology and personality in patients cured of Cushing's disease were explored by stepwise linear regression analysis. The standardized β-coefficients of this analysis were reported. The level of significance was set at $P \leq 0.05$.

Results

Sociodemographic and clinical characteristics

Patients cured of Cushing's disease and their matched controls

All patients (n=51) had been treated by transsphenoidal surgery, and 11 patients (22%) had been treated by additional radiotherapy because of persistent disease after surgery (Table 2). At the time of the current study, all patients were in remission and the mean duration of remission was 11±9yr (range 1–32yr, mode 3 and 5yr). Thirty-one patients (61%) were treated for some degree of pituitary insufficiency. Twenty-seven patients (53%) were substituted with hydrocortisone.

Patients treated for NFMA and their matched controls

All patients (n=55) had been treated by transsphenoidal surgery and 24 of these (43%) also by additional radiotherapy (Table 3). Mean duration of follow-up was 14±11yr (range 1–51yr, mode 4, 7, and 12yr). At the time of the current study, 51 patients (93%) were treated for pituitary insufficiency. Hydrocortisone substitution was used by 33 patients (60%).

Psychopathology

Patients cured of Cushing's disease versus their matched controls

Patients with long-term cure of Cushing's disease had a higher total score on the Apathy Scale ($t(85)=4.6$, $P<0.001$) and on the Irritability Scale ($t(77)=4.1$, $P<0.001$), compared with matched controls (Table 4). Patients also showed higher scores on the anxiety and depression subscales of the HADS ($t(82)=3.9$, $P<0.001$, and $t(78)=4.8$, $P<0.001$, respectively). On the MASQ-30, patients with long-term cured Cushing's disease scored higher on negative affect ($t(91)=3.5$, $P<0.001$) and somatic arousal ($t(78)=4.1$, $P<0.001$) and lower on positive affect ($t(95)=-3.7$, $P<0.001$). On the Apathy scale, 57% of the patients with Cushing's disease had a score of 14 or greater, and on the Irritability Scale, 31% of the patients had a score

Table 2 Clinical characteristics of patients cured of Cushing's disease and their matched controls

	Cushing's disease (n=51)	Matched controls (n=51)	P-value
Gender (male/female)	8/43	8/43	1.00
Age in yrs	53 (13)	54 (13)	0.70
Educational level (n)	Low: 20 Medium: 13 High: 18	Low: 18 Medium: 16 High: 17	0.80
Surgery, n (%)	51 (100%)	NA	NA
Postoperative radiotherapy, n (%)	11 (22%)	NA	NA
Duration of remission in yrs	11 (9)	NA	NA
Duration of follow-up in yrs	14 (10)	NA	NA
Hypopituitarism, n (%)	Any axis: 31 (61%) GH: 20 (39%) LH/FSH: 14 (28%) TSH: 21 (41%) ADH: 10 (20%)	NA	NA
Hydrocortisone substitution, n (%)	27 (53%)	NA	NA

Data are mean ± SD or number and %; NA=not applicable

of 14 or greater, indicative for the presence of clinically significant apathy and irritability, respectively. On the HADS, 26% of the patients with cured Cushing's disease scored greater than 8 on the depression subscale and 20% of the patients scored greater than 8 on the anxiety subscale. This is indicative for the presence of clinically relevant depression or anxiety, respectively. In particular, depression is evident in a substantial amount of the patients. Significantly more patients than controls had clinically relevant scores on these questionnaires (Apathy $P<0.001$; Irritability $P<0.001$; anxiety subscale HADS $P=0.014$; and depression subscale HADS $P=0.002$).

When patients with short-term (<10 yr, 28 patients (six males), aged 54±14yr) and long-term (≥10 yr, 23 patients (two males), aged 52±13yr) remission were compared, several differences were found. After a remission duration of more than 10yr, the patients scored significantly worse on the Apathy Scale ($P=0.002$), the depression subscale of the HADS ($P=0.033$), and the positive affect subscale of the MASQ-30 ($P<0.001$).

Patients treated for NFMA vs. their matched controls

Patients treated for NFMA had a higher total score on the Apathy Scale ($t(108)=3.0$, $P=0.003$) and higher mean scores on the anxiety and depression subscale of the HADS compared with their matched controls ($t(108)=-2.4$, $P=0.017$, and $t(108)=-4.7$, $P<0.001$, respectively), but the scores for the other scales (Irritability Scale and MASQ-30) were not different (Table 5). In patients treated for NFMA, a score of 14 or greater on the Apathy Scale was observed in 40%, a score of 14 or

Table 4 Psychopathology and personality traits in patients cured of Cushing's disease and their matched controls

	Cushing's disease (n=51)	Matched controls (n=51)	P-value
Apathy Scale			
Total score	14.8 (6.5)	9.8 (4.2)	**0.000**
Score ≥14, n (%)	29 (57%)	7 (14%)	**0.000**
Irritability Scale			
Total score	11.5 (7.7)	6.6 (4.2)	**0.000**
Score ≥14, n (%)	16 (31%)	2 (4%)	**0.000**
HADS			
Anxiety	6.2 (4.2)	3.5 (2.5)	**0.000**
Depression	5.6 (4.5)	2.1 (2.5)	**0.000**
Anxiety score >8, n (%)	10 (20%)	2 (4%)	**0.014**
Depression score >8, n (%)	13 (26%)	2 (4%)	**0.002**
MASQ-30			
Negative Affect	18.2 (6.7)	14.2 (4.8)	**0.001**
Positive Affect	25.7 (9.6)	32.1 (7.6)	**0.000**
Somatic Arousal	17.4 (6.6)	13.1 (3.7)	**0.000**
DAPP			
Submissiveness	19.0 (7.7)	15.4 (5.5)	**0.008**
Cognitive distortion	11.5 (5.6)	8.4 (2.6)	**0.001**
Identity problems	13.0 (6.6)	8.7 (3.3)	**0.000**
Affective lability	21.7 (7.8)	13.9 (4.7)	**0.000**
Stimulus seeking	14.6 (4.8)	13.6 (4.3)	0.260
Compulsivity	23.8 (6.6)	20.1 (6.1)	**0.004**
Restricted expression	21.2 (7.3)	18.0 (6.0)	**0.016**
Callousness	16.1 (4.5)	15.3 (4.4)	0.392
Oppositionality	22.9 (8.8)	17.2 (5.5)	**0.000**
Intimacy problems	18.8 (6.4)	20.5 (7.0)	0.188
Rejection	17.2 (5.7)	17.1 (6.0)	0.959
Anxiousness	15.3 (6.2)	11.1 (4.2)	**0.000**
Conduct problems	9.0 (1.8)	9.0 (1.6)	0.953
Suspiciousness	12.6 (5.9)	10.8 (3.0)	0.061
Social avoidance	12.3 (6.3)	9.8 (3.2)	**0.014**
Narcissism	15.0 (5.5)	13.3 (5.0)	0.091
Insecure attachment	13.3 (6.6)	10.7 (4.5)	**0.025**
Self-harm	7.3 (2.9)	6.5 (1.8)	0.110

Data are mean (SD), unless otherwise mentioned

greater on the Irritability Scale in 27%, a score greater than 8 on the HADS anxiety scale in 15%, and a score greater than 8 on the depression scale in 13%. There were significantly more patients than controls with a clinically relevant score on the HADS depression scale (P=0.026). There were no differences between patients with short-term (<10yr) and long-term (≥10yr) duration of follow-up.

Factors associated with psychopathology in patients cured of Cushing's disease
Stepwise linear regression analysis was performed using the absolute test scores of the patients with long-term cure of Cushing's disease as dependent variables and gender, age, education, hypopituitarism, hydrocortisone dependency, additional

Table 5 Psychopathology and personality traits in patients treated for NFMA and their matched controls

	NFMA patients (n=55)	Matched controls (n=55)	P-value
Apathy Scale			
Total score	12.8 (4.7)	10.2 (4.1)	**0.003**
Score ≥14, n (%)	22 (40%)	13 (24%)	0.065
Irritability Scale			
Total score	10.0 (5.8)	8.9 (5.1)	0.289
Score ≥14, n (%)	15 (27%)	10 (18%)	0.255
HADS			
Anxiety	5.0 (3.6)	3.5 (3.0)	**0.017**
Depression	4.6 (3.9)	1.7 (2.1)	**0.000**
Anxiety score >8, n (%)	8 (15%)	3 (6%)	0.105
Depression score >8, n (%)	7 (13%)	1 (2%)	**0.026**
MASQ-30			
Negative Affect	15.6 (5.8)	14.9 (5.8)	0.492
Positive Affect	29.3 (8.3)	30.4 (8.0)	0.491
Somatic Arousal	15.0 (5.7)	13.5 (4.4)	0.137
DAPP			
Submissiveness	16.5 (5.6)	17.1 (6.1)	0.636
Cognitive distortion	9.5 (3.9)	9.8 (4.9)	0.747
Identity problems	10.2 (4.5)	9.6 (4.3)	0.454
Affective lability	18.8 (5.6)	16.1 (5.6)	**0.013**
Stimulus seeking	14.5 (4.4)	14.2 (5.1)	0.748
Compulsivity	22.3 (6.9)	21.9 (6.6)	0.746
Restricted expression	21.9 (4.5)	20.2 (5.2)	0.080
Callousness	16.9 (4.6)	15.9 (4.3)	0.222
Oppositionality	20.3 (6.5)	19.1 (6.7)	0.378
Intimacy problems	20.1 (6.7)	19.3 (6.6)	0.566
Rejection	18.3 (5.8)	17.0 (5.9)	0.260
Anxiousness	12.8 (4.7)	12.9 (4.8)	0.905
Conduct problems	9.7 (2.8)	9.5 (2.4)	0.690
Suspiciousness	11.0 (3.5)	10.9 (4.0)	0.995
Social avoidance	11.3 (3.9)	10.7 (4.0)	0.374
Narcissism	15.6 (4.9)	15.4 (5.9)	0.902
Insecure attachment	13.0 (5.2)	13.1 (5.3)	0.928
Self-harm	6.9 (2.4)	6.4 (1.7)	0.228

Data are mean (SD), unless otherwise mentioned

radiotherapy, and duration of remission as independent variables. The total score on the Apathy Scale was negatively influenced by educational level (β=-0.380, P=0.009), which means that a higher education level predicts a lower score on the Apathy Scale in these patients. The total score on the Irritability Scale was positively associated with additional radiotherapy (β=0.314, P=0.034), which indicates that patients who had additional radiotherapy scored higher on the Irritability Scale. The depression subscale of the HADS was positively influenced by the duration of remission (β=0.358, P=0.015), meaning that a longer duration of remission indicates a higher score on the depression subscale of the HADS. On the MASQ-30, the positive affect subscale was positively influenced by gender (β=0.410, P=0.003), with females scoring higher, and education (β=0.338, P=0.012), with higher educational level predicting higher scores. The positive affect subscale was negatively associated with duration of remission (β=-0.332, P=0.014), with longer duration of remission indicating lower scores on this subscale. The negative affect subscale was negatively associated with gender (β=-0.361, P=0.014), with females scoring lower, and positively influenced by duration of remission (β=0.311, P=0.032), with longer duration of remission indicating higher scores on the negative affect subscale.

Personality

Patients cured of Cushing's disease versus their matched controls

Patients with long-term cure of Cushing's disease scored worse compared with matched controls on the DAPPs personality traits submissiveness (t (90)=2.7, P=0.008), cognitive distortion (t (71)= 3.6, P<0.001), identity problems (t (74)=4.2, P<0.001), affective lability (t (82)=6.1, P<0.001), compulsivity (t (100)=2.9, P=0.004), restricted expression (t (97)=2.5, P=0.016), oppositionality (t (84)=4.0, P<0.001), anxiousness (t (89)=4.0, P<0.001), social avoidance (t (74)=2.5, P=0.014), and insecure attachment (t (88)=2.3, P=0.025), see also Table 4. When using depression and anxiety as covariates, only two traits remained statistically different between patients and controls: affective lability (F (1)=16.3, P<0.001) and anxiousness (F (1)=5.2, P=0.024). This observation increases the likelihood of the presence of these premorbid traits. The traits identity problems (F (1)=3.1, P=0.081), compulsivity (F (1)=2.9, P=0.092), and intimacy problems (F (1)=2.9, P=0.094] showed trend significance. When only co-varying for depression, the traits affective lability (F (1)=15.5, P<0.001) and anxiousness (F (1)=5.7, P=0.019) remained significantly different between patients and controls, whereas the traits identity problems (F (1)=3.5, P=0.064), compulsivity (F (1)=3.3, P=0.071), oppositionality (F (1)=3.0, P=0.087), and intimacy problems (F (1)=3.1, P=0.079) showed trend significance. When patients with short-term (<10yr, 24 patients (17 men), aged 58±11yr) and long-term (≥10yr, 31 patients (13 men), aged 65±7yr) remission were

compared, only minor differences were found. After a remission duration of more than 10yr, the patients scored significantly worse only on the identity problems subscale (P=0.045) and the intimacy subscale (P=0.003) of the DAPPs.

Patients treated for NFMA vs. their matched controls

Patients treated for NFMA scored worse on the trait affective lability (t (108)=2.5, P=0.013) of the DAPPs compared with controls but not on other traits.

When patients with short-term (<10yr) and long-term (≥10yr) duration of follow-up were compared, patients with long-term follow-up scored higher on the intimacy subscale of the DAPPs (P=0.020), see also Table 5.

Factors associated with personality in patients cured of Cushing's disease

On the DAPPs questionnaire, several subscales were associated with the independent variables: the cognitive distortion subscale was negatively associated with education (β=-0.391, P=0.007), with higher education indicating lower scores on the cognitive distortion subscale. The identity problems subscale was positively influenced by additional radiotherapy (β=0.329, P=0.021) and hydrocortisone dependency (β=0.278, P=0.049), with additional radiotherapy and hydrocortisone dependency predicting higher scores. The rejection subscale was positively associated with education (β=0.426, P=0.003), with higher education being associated with higher scores on this subscale. The conduct problems subscale was negatively associated with gender (β=-0.331, P=0.024), with females scoring lower. The suspiciousness subscale was positively associated with hypopituitarism (β=0.302, P=0.042), which indicates that hypopituitarism is associated with higher scores on the suspiciousness subscale. Finally, the self-harm subscale was positively affected by duration of remission (β=0.370, P=0.011), with longer duration of remission being associated with higher scores on the self-harm subscale.

Comparison of Z-scores between patients cured of Cushing's disease and patients treated for NFMA

In comparison with patients treated for NFMA, patients with long-term cure of Cushing's disease had higher scores on the Apathy Scale (P<0.001), the Irritability Scale (P<0.001), and on the anxiety subscale of the HADS (P<0.001). Furthermore, patients with cured Cushing's disease scored higher on the negative affect (P<0.001) and on the somatic arousal (P<0.001) subscales of the MASQ-30, whereas they scored lower on the positive affect subscale (P<0.001). On the DAPPs, patients with cured Cushing's disease scored worse when compared with patients treated for NFMA on submissiveness (P=0.002), cognitive distortion (P<0.001), identity problems (P<0.001), affective lability (P<0.001), compulsivity (P=0.010), oppositionality (P<0.001), anxiousness (P<0.001), conduct problems

Comparison of psychopathology of patients with Cushing's disease and patients with NFMA by Z-scores

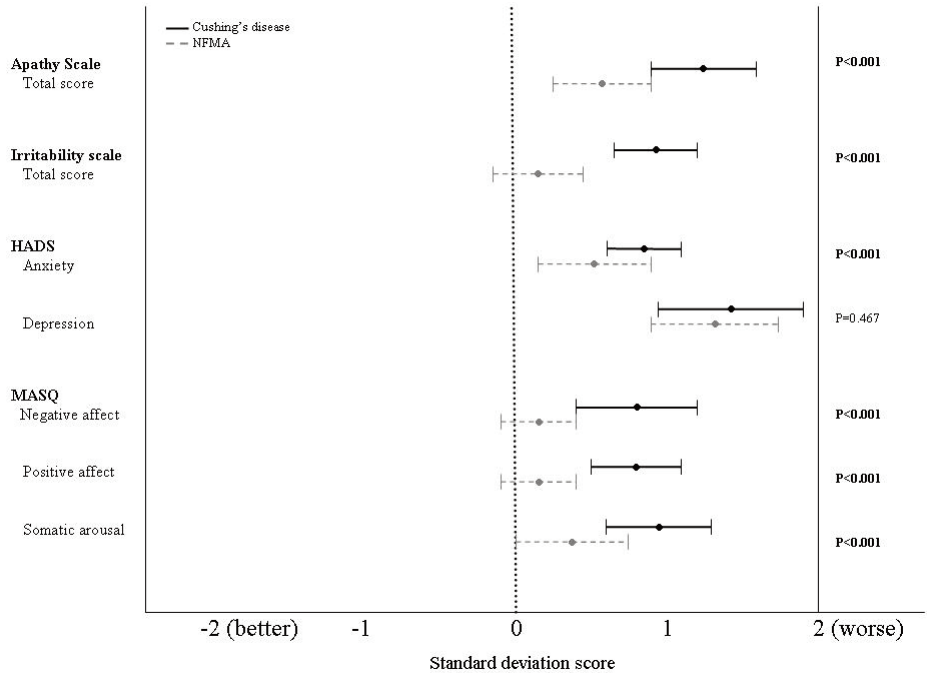

Figure 1: *Figure 1: Z-scores of patients cured from Cushing's disease and of patients treated for NFMA, calculated for each patient group by comparison with their own matched control groups. Z-scores with 95% confidence intervals are shown in this figure. The zero Z-line indicates the scores of the matched controls. On the apathy scale, irritability scale, anxiety subscale of the HADS, and all three subscales of the MASQ-30 patients with long-term cured Cushing's disease scored worse when compared with patients with treated NFMA.*

(P<0.001), suspiciousness (P=0.049), social avoidance (P=0.049), and insecure attachment (P=0.019). This is also shown in Figure 1 and Figure 2.

Discussion

This study demonstrates that patients with long-term cure of Cushing's disease suffer from more psychopathology and maladaptive personality traits compared with matched controls. In addition, patients with long-term cure of Cushing's disease had significantly more psychopathology and maladaptive personality traits than patients previously treated for NFMA, indicating that the presence of psychopathology and maladaptive personality traits was not merely related to pitu-

Comparison of personality traits (DAPPs) of patients with Cushing's disease and patients with NFMA by Z-scores

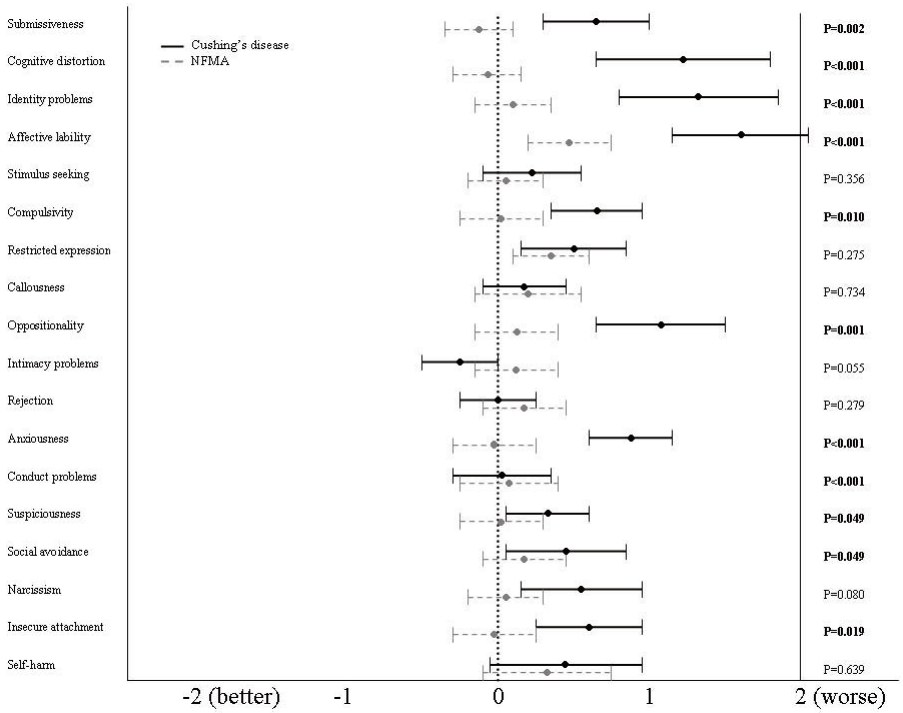

Figure 2*: Z-scores of patients cured from Cushing's disease and of patients treated for NFMA. Patients with long-term cured Cushing's disease scored worse when compared with patients with treated NFMA on the DAPP subscales submissiveness, cognitive distortion, identity problems, affective lability, compulsivity, oppositionality, anxiousness, conduct problems, suspiciousness, social avoidance, and insecure attachment.*

itary tumors and/or their treatment in general. Therefore, the long-term effects of cured Cushing's disease on psychopathology and personality traits are more likely to be the consequence of previous glucocorticoid excess. These observations point to irreversible effects of previous glucocorticoid excess on the central nervous system. Psychopathology is reported to be present in the majority of patients with active Cushing's disease (17). Major depression, atypical depression, or at least one other psychiatric diagnosis, is present in more than 50% of these patients (18–23). Appropriate treatment of hypercortisolism results in improvement of these symptoms in many of these patients (2, 3, 24), and the prevalence of overall psychopathology decreases to 24% of the patients within 1yr after appropriate treatment of active Cushing's disease (21, 22). Therefore, appropriate treatment of Cushing's disease results in improvement of the psychiatric manifestations asso-

ciated with this disease.

Several previous studies evaluated the effects of Cushing's disease and Cushing's syndrome on psychopathology and personality traits. These studies are summarized in Table 1. Several previous studies in patients with active Cushing's disease concluded that patients had a higher tendency for anxiety than controls (6, 19, 25). In contrast, Kelly *et al.* (3) concluded that patients with active Cushing's syndrome and control patients scored equally on personality traits (neuroticism and extraversion). When patients with Cushing's syndrome were reassessed after appropriate treatment, there was a significant decrease in neuroticism score but not extraversion. However, another recent study concluded that were no differences in personality traits between patients with Cushing's syndrome in remission and controls (7). Therefore, maladaptive personality traits are documented after treatment of Cushing's disease in some, but not all, studies. However, these studies included only limited numbers of patients with heterogeneous clinical characteristics. Moreover, the long-term effects of cure of Cushing's disease have not been studied in detail.

A limitation of the present study was the cross-sectional study design instead of a longitudinal design. Consequently, we do not have any information on premorbid functions, the effects of active Cushing's disease, and the extent of reversibility of the disturbed parameters. Nonetheless, these observations do not invalidate our observations that patients with long-term cure show an increased prevalence of psychopathology and maladaptive personality traits compared with matched controls and with patients treated similarly for NFMA. It might be argued that the use of mailed self-rating scales for depression and anxiety is a limitation. However, self-reported scales provide a valuable tool to measure the patients' perception of their illness, which is not possible with observer ratings (26). Furthermore, we intended to screen for symptoms of possible psychopathology, not to establish psychopathology. Another possible limitation is the fact that the most distressed subjects are the ones who are more likely participate. Unselected series (3, 7, 22) reported a prevalence of psychopathology of 24–32% in patients cured from Cushing's disease, which is in accordance with data of the present study.

Patients with long-term cure of Cushing's disease provide a unique human model to study the effects of prolonged, but transient (endogenous), glucocorticoid excess. Furthermore, the results of the current study may be relevant for patients who have previously been treated with prolonged high doses of glucocorticoids (27, 28).

In summary, patients with long term cure of Cushing's disease report a high prevalence of psychopathology, compared with both matched controls and patients previously treated for NFMA. Furthermore, patients with long-term cure of Cush-

ing's disease have a greater degree of maladaptive personality traits. The results suggest that these observations reflect irreversible effects of previous glucocorticoid excess on the central nervous system rather than an effect of pituitary tumors and/or their treatment in general.

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Chapter 7

Neuropsychiatric disorders in Cushing's syndrome

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Abstract

Glucocorticoids are crucial in the initiation and consolidation of the stress response. Patients with active Cushing's syndrome (CS) are exposed to excessive endogenous glucocorticoid levels. In these patients, psychopathology is often being observed. The most common co-morbid disorder is major depression, but to a lesser extent mania and anxiety disorders have also been reported. A severe clinical presentation of CS often also includes depression. Reduction of glucocorticoid synthesis or action, either with metyrapone, ketoconazole, or mifepristone, rather than treatment with antidepressant drugs, is generally successful in relieving depressive symptoms, as well as other disabling symptoms. Following successful surgical treatment of hypercortisolism, both physical and psychiatric signs and symptoms improve substantially. However, it appears that patients do not completely return to their premorbid level of functioning and persistent impairment of quality of life and cognitive function has been reported despite long-term cure. At present, it is not clear whether, and to which extent, psychopathology still affects general well-being after long-term cure of CS.

Introduction

Cushing's syndrome (CS) is associated with psychopathology. The spectrum of behavioral abnormalities observed in patients with CS ranges from severe depression to mania and can be present in both endogenous CS and in patients exposed to exogenous corticosteroids, which strongly suggests a causal role for corticosteroid excess in the initiation and consolidation of psychopathology. In this concise review, we will address the pathophysiology of the neuropsychiatric disorders observed in CS. In order to emphasize the crucial role of corticosteroid excess in the control of mood and behavior and cognitive function, we will first discuss the data on psychopathology observed in active CS, then the effects of reduction of corticosteroid synthesis or action on psychopathology in CS, and, finally, the reversibility of psychopathology after remission of glucocorticoid excess.

Physiology and pathophysiology of the control of behavior in response to stress

In order to put the behavioral abnormalities observed in CS into the right perspective, it is important to realize that cortisol (or corticosterone in the rodent) is the main mediator of the stress response (1) . When an individual is exposed to a stressor, rapid changes occur within seconds to minutes through stimulation of the sympathetic nervous system via catecholamines (CRH, AVP) and via nongenomic actions of cortisol. These mediators increase excitability, resulting in behavioral changes characterized by increased vigilance, alertness, arousal, and attention. In addition, the stress response is characterized by slower changes that occur within minutes to hours via stimulation of both the mineralocorticoid (MR) and glucocorticoid (GR) receptor. All these changes, in the end, occur only with the purpose to induce the required behavioral adaptations for the individual to be able to adequately cope with the stressor. However, when the stressor becomes chronic, a so-called vulnerable phenotype develops, characterized by neurodegenerative changes within the central nervous system and cognitive impairment (1). Thus, it is not surprising that CS, that can be considered the clinical human equivalent for severe chronic stress, is associated with behavioral abnormalities.

Psychopathology in active Cushing's syndrome

Active, untreated CS is associated with a high prevalence of psychopathology. The frequencies of psychiatric symptoms have been evaluated since the late 1970s using different criteria in a total of approximately 500 patients with CS, mostly comprising small patient groups. A subset of these studies that evaluated psychopathology and personality traits are summarized in Table 1 .

An early study on personality traits in 53 patients with CS reported that 60% of these subjects had personality changes (2). However, it is not clear from the data

Table 1: Overview of studies on psychopathology and personality traits in patients with Cushing's disease and Cushing's syndrome

Author, year	Number of subjects	Gender (m/f)	Age yr (SD)	Active/treated	Methods	Outcomes
Starr, 1951 (2)	53 Cushing's syndrome	NA	NA	NA	NA	Of all patients, 35% had marked personality alterations, and 25% showed frank psychosis which resulted in institutionalization.
Cohen, 1980 (6)	29 Cushing's syndrome	7/22		Almost all were seen during admission for diagnosis. A few were first seen immediate after OK	Interviews. Detailed clinical history and an examination of mental state	Of all patients, 86% had distinct affective disorders. Twenty five patients suffered from depression, and one had manic and depressive episodes.
Sablowski, 1986 (3)	9 Cushing's disease 9 Acromegaly 6 Prolactinoma 24 Controls	Not given	NA	Before and after surgery	Freiburger Personality Inventory, Gießen test, State-trait-anxiety inventory	Pre-operative, there is a tendency to higher scores of trait-anxiety in pituitary patients compared to controls. This did not change after surgery. Furthermore, Cushing's disease patients seemed more nervous and restrained than acromegaly patients.
Kelly, 1996 (4)	43 Cushing's syndrome 24 acromegaly and prolactinoma	10/33	NA	Prospective study. Before and after treatment	Present state examination, Hamilton rating scale Crown-Crisp experiential index, Eysenck personality inventory	Present state examination: only 19% of the active Cushing's syndrome patients were normal, whereas 87% of the controls were normal. Depression and all scales of the Crown-Crisp improved after treatment. When patients were re-assessed after appropriate treatment, there was a significant decrease in neuroticism score but no change in extraversion.
Dorn, 1995 (20	33 Cushing's syndrome 17 Matched hospitalized controls	5/28	36±9	Hypercortisolaemic during interview	Interviews, Atypical depression diagnostic scale, Hamilton rating scale, self-report instruments, medical records information	Anytime during the active phase, 67% of the patients had at least one diagnosis. Atypical depression was the most frequent finding (52%). The duration of CS was an important factor in predicting whether patients sought psychological intervention.
Dorn, 1997 (15)	33 Cushing's syndrome	5/28	36±9	Before and 3, 6, en 12 months after correction for hypercortisolism	Interviews, Atypical depression diagnostic scale, Hamilton rating scale, self-report instruments, medical records information	Before cure, 67% had significant spychopathology. After cure, overall psychopathology decreased to 54% at 3 months, 36% at 6 months, and 24% at 12 months. There was an inverse correlation between psychological recovery and baseline morning cortisol. Atypical depression remained the most frequent finding.

Flitsch, 2000 (21)	19 Cushing's disease 18 Acromegaly 11 NFMA	7/12	34±12	Before and after (6 months) transsphenoidal microsurgery	Semi-structured interview, Reiburger Personlichkeitsinventar, State-trait-anxiety-inventory, Rosenzweig picture frustration test, Befindlichkeitsskala, Giessener Beschwerdebogen	Most common psychopathological signs were excitability and depression. At least one of these signs was found in 12 out of 19 Cushing's disease patients. Six-eight months after surgery, majority of the Cushing's disease patients (10 of 19) noticed an increase in physical well-being.
Sonino, 2006 (7)	24 Cushing's syndrome 24 Healthy matched controls	5/19	35±11	1-3 yrs in remission	Tridimensional personality questionnaire, Symptom rating test	No significant differences in personality dimensions between patients and controls. On the Symptom rating test, patients scored higher on anxiety, depression and psychotic symptoms compared to controls.

in that study whether these patients still had active Cushing's disease. Another study in 9 patients with active Cushing's disease concluded that patients had a higher tendency for anxiety than controls (3). In contrast, Kelly et al. (4) concluded that patients with active CS and control patients scored equally on personality traits (neuroticism and extraversion). Starkman and Schteingart (5) evaluated the prevalence of psychiatric symptoms in 35 patients with active CS and found that irritability, depressed mood, and anxiety were present in the majority of the patients. Intriguingly, an increased overall psychiatric disability, measured by and indicated by a specific score, was associated with increased cortisol secretion. Among another consecutive unselected series of 29 patients with untreated CS, 25 (86%) were significantly depressed. In this study, the severity of the depression was not related to circulating cortisol levels, but the depression was rapidly relieved when the tumor or adrenal glands were removed (6). Kelly *et al.* (7) compared in another study 15 patients with active CS both with 15 other patients who had been treated successfully for CS and with 13 patients with other pituitary tumors. Depression was the main psychiatric diagnosis using the CATEGO program after Present State Examinations. Patients with active CS were significantly more depressed (Hamilton Rating Scores) than were the other patients. Another study (8) compared 20 patients with Cushing's disease with 20 patients with major depressive disorder using the Structured Clinical Interview for DSM-III-R (SCID) and Research Diagnostic Criteria. A diagnosis of generalized anxiety disorder, major depressive disorder, or panic disorder, either alone or in combination, was present in approximately two thirds of the patients with Cushing's disease. Interestingly, behavioral symptoms usually first occurred at or after the onset of the first physical symptoms. However, the onset of panic disorder was associated with more chronic stages of active Cushing's disease. In agreement with the studies that involved small patient numbers, psychopathology was highly prevalent in a large cohort of 162 patients with Cushing's disease reported by Sonino *et al.* (9). Major depression, according to DSM-IV criteria, was present in more than 50% of the patients. Interestingly, the presence of psychopathology was significantly associated with older age, female gender, higher pretreatment 24-hour urinary cortisol levels, a more severe clinical condition, and absence of pituitary adenoma (Table 2). This has led to the inclusion of mood disorders in a clinical index for rating the severity of CS (10).

Effects of reduction of corticosteroid synthesis or action on psychopathology in Cushing's syndrome

Only a few studies with a limited number of patients have reported the effects of successful reduction of corticosteroid excess on psychopathology. These studies demonstrate that both reduction of corticosteroid synthesis with ketoconazole or

Table 2 Demographic and clinical correlates of major depression in pituitary-dependent Cushing's disease (reproduced with permission from Sonino *et al.* (9) and S. Karger AG, Basel)

	Non-depressed patients (n=74)	Depressed patients (n=88)	P-value[1]
Mean age (± SD), years	34.5 ± 13.5	40.0 ± 11.4	<0.01
Sex, male/female	26/48	12/76	<0.01
Urinary cortisol, nmol/day	1,076 ± 786	1,694 ± 1,170	<0.001
Plasma ACTH, pmol/l	15.9 ± 9.4	18.8 ± 12.2	NS
Clinical presentation, mild/severe	62/12	12/76	<0.001
Pituitary lesion[2], adenoma/no adenoma	45/8	41/21	<0.05

NS, not significant; 1, by χ^2 or t test; 2, data available in 115 cases

metyrapone and blockade of the glucocorticoid receptor with mifepristone positively affect psychopathology. The first study that reported the effects of medical treatment of patients with CS was published in 1979 (11). In this study, in 38 patients with CS, 65% were diagnosed with depression of different clinical severity. The majority of the patients were treated with metyrapone which resulted in remission of psychiatric symptoms in virtually all of them (11). This impressive treatment efficacy was later confirmed in another study with 53 patients with Cushing's disease pretreated with metyrapone and 24 patients who had been given pituitary irradiation for a median duration of 27 months (12). In contrast to metyrapone, a total of only 20 patients with CS have been reported that were treated with the GR antagonist mifepristone. The clinical applicability and effectivity of mifepristone in these CS patients was reviewed recently (13). Treatment with mifepristone resulted in a dramatic improvement of clinical signs in 15/20 patients. In parallel, in 3 of the 4 patients with psychopathology a significant improvement was reported. It is important to note that the beneficial effects of mifepristone on psychopathology already occur within a few days after the initiation of treatment.

Reversibility of psychopathology after remission of Cushing's syndrome

The literature is even scarcer when the potential reversibility of psychopathology after successful surgical treatment of CS is considered. The paucity of data after treatment indicates that a significant improvement occurs within the first year after treatment. Starkman *et al.* (14) reported significant improvement in both the depressed mood score and the modified Hamilton depression score in 23 patients with pituitary-dependent CS after treatment, which were also significantly correlated to decreases in urinary cortisol excretion. The longitudinal course of psychopathology in CS after correction of hypercortisolism was evaluated in 33 patients with active CS before and 3, 6 and 12 months after successful surgery.

Before cure, 67% of the patients had significant psychopathology, predominantly atypical depressive disorder and/or major affective disorder. After cure, overall psychopathology decreased significantly to 54% at 3 months, 36% at 6 months, and 24% at 12 months, when there was a parallel recovery of the hypothalamic-pituitary-adrenal axis (Figure 1). The authors also found an inverse correlation between psychological recovery and baseline morning cortisol. Intriguingly, even after correction of hypercortisolism, atypical depressive disorder continued to be the prevailing diagnosis, whereas the frequency of suicidal ideation and panic disorder increased (15). In our Leiden series of patients treated for Cushing's disease, we have documented persistent psychopathology in CS even after long-term remission for a mean of 13 years using general health-related questionnaires, like the Hospital Anxiety and Depression Scale (HADS) and the Nottingham Health Profile (NHP) (16). Noteworthy, some but not all items were no longer significant when corrected for hypopituitarism, indicating that hypopituitarism per se also importantly influences psychological well-being. The general clinical impression, however, is that the final outcomes of treatment of CS are far from satisfactory (17). In agreement, we recently documented in our Leiden cohort of 74 patients treated for Cushing's disease that cognitive function, reflecting memory and executive functions, was persistently impaired despite long-term cure. Compared with patients that had been treated for nonfunctioning pituitary macroadenomas (NFMA), patients cured from Cushing's disease had lower scores on the Mini Mental State Examination, and on the memory quotient of the Wechsler Mem-

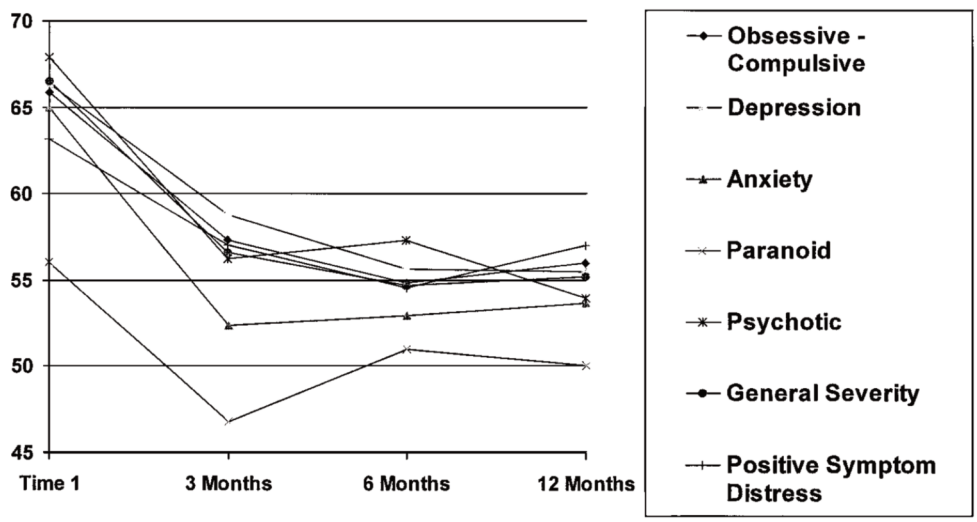

Figure 1 *Significant changes in mean T-scores of subscales of the Symptom Checklist-90R for patients with CS during CS (time 1) and 3, 6, and 12 months after treatment.*
Dorn et al. (15); copyright 1997, The Endocrine Society, with permission.

ory Scale. Furthermore, patients cured from Cushing's disease tended to recall fewer words on the imprinting, immediate recall, and delayed recall trials of the Verbal Learning Test of Rey. Patients cured from Cushing's disease also had lower scores on the Rey Complex Figure Test on both trials compared with NFMA patients. Finally, patients cured of Cushing's disease also made fewer correct substitutions (on the Letter-Digit Substitution Test) and came up with fewer correct patterns (on the Figure Fluency Test) compared with treated NFMA patients (18). These observations indicate irreversible effects of previous hypercortisolism on cognitive function and, thus, on the central nervous system.

Furthermore, in some, but not all, studies (2, 4, 19–21) maladaptive personality traits were documented after treatment for Cushing's disease. When patients with CS were re-assessed after appropriate treatment, there was a significant decrease in neuroticism score but no change in extraversion (4). However, another recent study concluded that there were no differences in personality traits between patients with CS in remission and controls (19). Therefore, maladaptive personality traits are documented after treatment of Cushing's disease in some, but not all, studies. However, definite conclusions on the extent of normalisation of mood and behavior cannot be drawn from these studies because they included only limited numbers of patients with heterogeneous clinical characteristics. Moreover, the long-term effects of cured Cushing's disease have not been studied in detail.

Conclusion

Active CS is associated with a high prevalence of psychopathology, mainly atypical depression. Treatments with glucocorticoid reducing or blocking agents can rapidly relief symptoms. After successful surgery, psychopathology decreases but mood and behavior do not seem to normalize. After long-term remission, patients with Cushing's disease still show decreased quality of life and impaired cognitive function. Future studies should aim at further investigating if and how CS longitudinal changes affect (subclinical) psychopathology.

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Chapter 8

Increased psychopathology and maladaptive personality traits, but normal cognitive functioning, in patients after long-term cure of acromegaly

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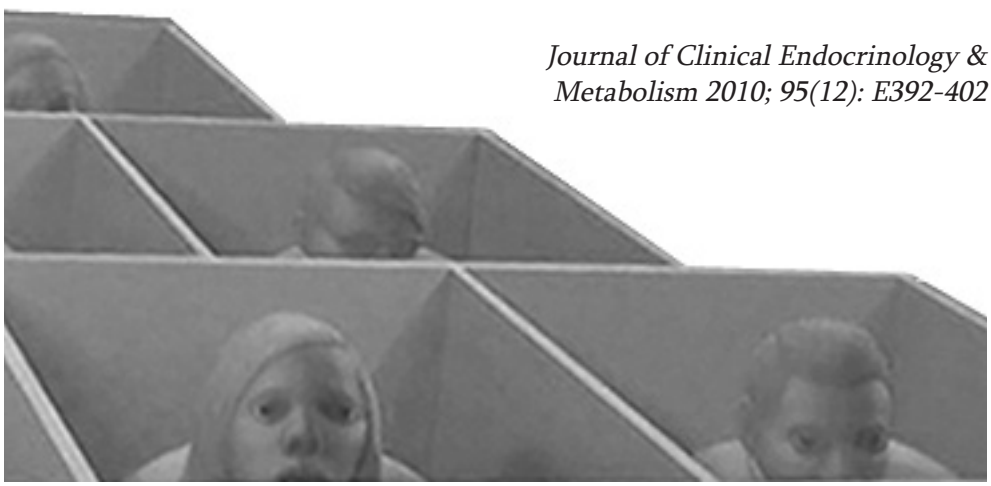

Abstract

Objective: Active acromegaly is associated with psychopathology, personality changes, and cognitive dysfunction. It is unknown whether, and to what extent, these effects are present after long-term cure of acromegaly.

Aim: The aim of the study was to assess psychopathology, personality traits, and cognitive function in patients after long-term cure of acromegaly.

Design: This was a cross-sectional study.

Patients and Methods: We studied 68 patients after long-term cure (13±1yr) of acromegaly and 68 matched controls. We compared these data with 60 patients treated for nonfunctioning pituitary macroadenomas (NFMAs) and 60 matched controls. Psychopathology was assessed using the Apathy Scale, Irritability Scale, Hospital Anxiety and Depression Scale, and Mood and Anxiety Symptoms Questionnaire short-form, and personality was assessed by the Dimensional Assessment of Personality Pathology short-form (DAPPs). Cognitive function was assessed by 11 tests.

Results: Compared with matched controls, patients cured from acromegaly scored significantly worse on virtually all psychopathology questionnaires and on several subscales of the DAPPs. Compared with NFMA patients, patients cured from acromegaly scored worse on negative affect ($P=0.050$) and somatic arousal ($P=0.009$) and seven of 18 subscales of the DAPPs ($P<0.05$). Cognitive function in patients cured from acromegaly did not differ from matched controls or patients treated for NFMA.

Conclusion: Patients with long-term cure of acromegaly show a higher prevalence of psychopathology and maladaptive personality traits but not cognitive dysfunction, compared with matched controls and patients treated for NFMA. These results suggest irreversible effects of previous GH excess, rather than effects of pituitary adenomas per se and/or their treatment, on the central nervous system.

Introduction

Acromegaly is associated with typical signs and symptoms caused by excess of GH and IGF-I. Almost 60yr ago, Bleuler (1, 2) reported that patients with active acromegaly and acromegalic patients after radiotherapy were often dull and apathetic and sometimes had an irritable mood. Subsequently other studies documented that patients with active acromegaly suffer from cognitive dysfunction, personality changes, and various forms of psychopathology (3–7). These observations suggest that the central nervous system is also involved in the clinical syndrome of active acromegaly. This notion is supported by the presence of GH receptors in various brain areas outside the classical pathways of the GH-IGF-I axis (8). Some of these structures are crucial for cognitive function and influence mental status and personality through connections with the limbic system and frontal lobe (9).

Many of the systemic changes induced by previous excess of GH and/or IGF-I are not completely reversed on successful biochemical treatment of active acromegaly (10), which may also be true for the effects of GH and/or IGF-I on the central nervous system. For instance, 36% of the patients with long-term cure of acromegaly showed elevated scores for anxiety and depression (11). We hypothesized that some of the effects of GH and/or IGF-I excess on the central nervous system might be irreversible. Therefore, the aim of the present study was to assess whether previous GH and/or IGF-I excess is associated with psychopathology, maladaptive personality traits, and cognitive dysfunction. We compared psychopathology, personality traits, and cognitive function between patients with long-term cure of acromegaly and gender-, age-, and education-matched controls. To assess to what extent treatment of pituitary adenomas per se affected our parameters, we additionally compared patients with long-term cure of acromegaly to patients treated for nonfunctioning pituitary macroadenomas (NFMAs).

Patients and Methods

Patients

We included four groups of subjects: 1) patients with long-term cure of acromegaly, and 2) age-, gender-, and education-matched control subjects for these patients with previous acromegaly, 3) patients previously treated for NFMA, and 4) age-, gender-, and education-matched control subjects for the patients previously treated for NFMA. The inclusion of two separate control groups was necessary because patients with acromegaly and patients treated for NFMA differ with respect to age and distribution of level of education.

Inclusion criteria were a history of acromegaly or NFMA, treatment by transsphenoidal surgery, age above 18yr, and remission of acromegaly defined by strict biochemical criteria (12). Exclusion criteria were a low Mini-Mental State Examination (MMSE) score, present or previous drug or alcohol abuse, and neurological disorders, not related to acromegaly or NFMA, because of potential interference with mental status, personality, and cognition.

We asked all eligible patients followed up in our institution to participate. Each patient was asked to provide a control subject of comparable gender, age, and educational level. When patients did not respond to our invitation within 3 wk, we encouraged them by phone to participate. The response rate was 93%. Of all patients (n=164) who were contacted to participate in this study, 92 patients were interested, of whom 68 completed all questionnaires and cognitive tests. Sixty patients preferred not to participate, and 12 patients did not respond. The clinical characteristics of the patients who did not participate were not different from those of the participating patients. Reasons for not participating were remote distance to our institution, participation in other studies, old age, and debilitating disease. None of the subjects stopped participation during the study at a later stage.

The diagnosis of acromegaly had been established by clinical signs and symptoms and biochemical tests, including impaired suppression of GH during glucose tolerance test and increased IGF-I levels for age. Cure of acromegaly was defined by normal serum IGF-I levels for age and serum GH levels less than 1.9μg/l for all patients and, in patients without somatostatin analog treatment, also by normal suppression of GH levels (<0.38μg/liter) during a glucose tolerance test (13). Remission was confirmed by repeating the tests at yearly intervals. Patients were followed up at our outpatient department, and pituitary hormone replacement was prescribed dependent on the results of the yearly evaluation of pituitary functions (see below).

In addition, we invited 133 patients previously treated by transsphenoidal surgery for nonfunctioning pituitary macroadenomas to participate. Each patient was asked to provide a control of comparable gender, age, and educational level, who was evaluated on the same day as the patient. The response rate was 96%. Eighty-four patients agreed to participate in this study, of whom 60 filled out all questionnaires and completed all cognitive tests. Forty-three patients preferred not to participate, and six patients did not respond. There were no differences in clinical characteristics between the patients who decided to participate and those who decided not to participate. None of the subjects stopped participation during the study at a later stage.

Pituitary function was assessed in patients treated for acromegaly or NFMA at yearly intervals by experienced clinical endocrinologists. This evaluation consisted of measurement of free T_4 and testosterone/SHBG (male patients) levels. If

these laboratory results were below the lower limit of the respective reference ranges, substitution with L-T_4 and/or testosterone was prescribed. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was prescribed. Corticotrope function was assessed by appropriate stimulation tests, including a CRH stimulation test or an insulin tolerance test. Normal cortisol reserve was defined by stimulated cortisol concentrations greater than 550nmol/l. In cortisol-deficient patients, the hydrocortisone dose was on average 20mg/d divided into two to three dosages. Evaluation of GH deficiency was performed by an insulin tolerance test and/or a GHRH-arginine test, only in patients under the age of 70yr and only after at least 2yr of remission. In NFMA patients with inadequate stimulation of GH levels by one of these tests, treatment with recombinant human (rh) GH was prescribed, aiming at IGF-I levels between 0 and +2 SD values. Patients previously treated for acromegaly were tested with the same tests (14), but in case of GH deficiency, these patients were treated with rhGH from 2005 onward during a controlled trial of rhGH replacement (15).
The protocol was approved by the Medical Ethics Committee of the Leiden University Medical Center, and written informed consent was obtained from all subjects.

Study design

The study consisted of a single study visit, during which each participant participated in a structured interview and performed the cognitive tests. Furthermore, patients and controls were asked to complete five questionnaires on psychopathology and personality traits at home and to return these in a prepaid envelope.

Questionnaires

Apathy Scale

Apathy was assessed by the Apathy Scale that consists of 14 questions on a 4-point scale measuring different features of apathy in the 2 previous weeks. The total score of this scale ranges from 0 to 42 points, with higher scores indicating greater apathy. Apathy is defined by a total score of 14 points or more (16, 17).

Irritability Scale

Irritability was assessed by the Irritability Scale that consists of 14 items on a 4-point scale, which assesses different features of irritability in the 2 previous weeks. The total score ranges from 0 to 42 points, with higher scores indicating greater irritability. Irritability is defined by a total score of 14 points or more (17).

Hospital Anxiety and Depression Scale (HADS)
Anxiety and depression were assessed by the HADS that consists of 14 items on a 4-point scale. Both anxiety and depression subscale scores range from 0 to 21 points. Higher scores indicate more severe anxiety and/or depression. Anxiety or depression is defined by total scores more than 13 points on the respective subscales (18, 19).

Mood and Anxiety Symptoms Questionnaire short-form (MASQ-30)
The MASQ-30 consists of 30 items to assess symptoms of mood and anxiety disorders subdivided into the three subscales: negative affect, lack of positive affect, and somatic arousal. The scores of each subscale range from 10 to 50, with higher scores indicating more severe negative affect, more positive affect, or more somatic arousal. There are no formal cutoff scores for these subscales (20, 21).

Dimensional Assessment of Personality Pathology short-form (DAPPs)
The DAPPs consists of 136 items assessing personality 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, and higher scores indicate more pronounced maladaptive personality traits. There are no formal cutoff scores for these subscales (22, 23).

Cognitive evaluation

Cognitive tests were used to assess the full spectrum of cognitive functioning. A functional classification was used to subdivide the 11 tests into the cognitive domains global cognitive functioning, memory, and executive functioning (24). The psychological evaluation took approximately 1.5handwasperformed in a predefined order. None of the patients required more than one session to complete all tests. The following tests were used: MMSE, Wechsler Memory Scale, Verbal Learning Test of Rey, Rey Complex Figure Test, Trail-Making Test, Stroop Color-Word Test, Letter-Digit Substitution Test, Digit-Deletion Test, Figure Fluency Test, FAS test, and the synonyms subtest of the Groninger Intelligence Test-2 (32–41).The description of these tests is included as an online supplement, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org.

Statistical analysis

Data were analyzed using PASW Statistics version 17.0.2 (SPSS Inc., Chicago, IL, USA). All data were presented as mean ± SD, unless mentioned otherwise. The primary analysis comprised the comparison of the results between patients cured of acromegaly and their matched controls and between the patients with NFMA and their matched controls. Groups were compared using a linear mixed model, with the matched patient-control pairs as random factor. For the clinical characteristics, a nonparametric χ^2 test was used in case of categorical data, and the Mann-Whitney test was used in case of continuous variables. Secondary analysis comprised the comparison of results in relation to patient and treatment characteristics. To compare patients treated for acromegaly and patients treated for NFMA, mean and SD scores for each questionnaire subscale were calculated for each control group, and subsequently Z-scores were calculated for each patient group in relation to their appropriate control group. The Z-scores were compared using a general linear model, with additional radiotherapy and hypopituitarism as fixed factors. Odds ratios were calculated using the (ad)/(bc) formula. The odds ratios represent the odds of a score above the cutoff score in a specific questionnaire in the acromegaly or NFMA group to the odds of a score above the cutoff score in the matched controls. Independent variables affecting psychopathology and personality in patients cured of acromegaly were explored by stepwise linear regression analysis. The standardized β-coefficients of this analysis were reported. The level of significance was set at $P \leq 0.05$.

Results

Patient characteristics

Patients with long-term cure of acromegaly

All patients (n=68) had been treated by transsphenoidal surgery and 15 patients (22%) had been treated by additional radiotherapy. Eleven patients (16%) were treated by somatostatin analogs, and two patients (3%) received pegvisomant therapy. All patients were in biochemical remission. Twenty-one percent of the patients had suffered from a microadenoma, 54% from a noninvasive macroadenoma, and 21% from an invasive macroadenoma. The mean duration of active disease before treatment was 7.4±0.7yr, whereas the mean duration of remission was 13.1±1.0yr. Mean GH levels before operation were 96±16μg/liter and mean IGF-I SD adjusted for gender and age was 8.5±0.8. The GH concentrations preoperatively are derived from the mean of four samples obtained with 30-min intervals during 2h (Table 1).

At the time of the current study, 29 patients (43%) required treatment for pitu-

Table 1 Clinical characteristics of patients with long term cure of acromegaly and of patients previously treated for NFMA

	Acromegaly patients (n=68)	NFMA patients (n=60)
Gender (male/female)	35/33	34/26
Age in years	59 (11)	62 (10)
Education (n)	Low: 34	Low: 20
	Medium: 8	Medium: 23
	High: 26	High: 17
Transsphenoidal surgery, n (%)	68 (100%)	60 (100%)
Additional radiotherapy, n (%)	15 (22%)	27 (45%)
Somatostatin analogue therapy, n (%)	11 (16%)	NA
Pegvisomant therapy, n (%)	2 (3%)	NA
Duration active disease, yr (se)	7.4 (0.7)	NA
Duration of remission/follow-up, yr (se)	13.1 (1.0)	13.5 (1.4)
Hypopituitarism, n (%)	Any axis: 29 (43%)	Any axis: 56 (93%)
	GH: 16 (24%)	GH: 46 (77%)
	LH/FSH: 13 (19%)	LH/FSH: 34 (57%)
	TSH: 17 (25%)	TSH: 40 (67%)
	ACTH: 21 (31%)	ACTH: 40 (67%)
GH level before operation (se)	96 µg/liter (16)	NA

Data are mean ± SD unless otherwise mentioned, NA; not applicable, se; standard error of the mean

itary insufficiency, and 16 patients (24%) were treated for GH deficiency with rhGH. There were no differences between patients and controls in gender, age, and education level. During the interview, 44% of the patients reported memory problems in daily life, and 25% reported problems in executive functioning.

Patients treated for nonfunctioning pituitary macroadenomas

All patients (n=60) had previously been treated by transsphenoidal surgery and 27 patients (45%) also by postoperative radiotherapy. Fifty-six patients (93%) required treatment for pituitary insufficiency, and 46 NFMA patients (77%) were on rhGH replacement therapy. There were no differences between patients and controls in gender, age, and education level (Table 1). During the interview, 37% of the patients reported memory problems in daily life, and 27% reported problems in executive functioning.

Psychopathology, personality traits, and cognitive function

Patients with long-term cure of acromegaly versus their matched controls

Patients with long-term cure of acromegaly scored worse compared with matched controls on the Apathy Scale (P=0.001), the Irritability Scale (P=0.006), the anxiety and depression subscales of the HADS (P=0.031, and P=0.003, respectively), and the somatic arousal subscale of the MASQ-30 (P=0.042). There were no differences on the negative and positive affect subscales of the MASQ-30 between pa-

tients and controls. Furthermore, patients with cured acromegaly scored worse on the affective lability (P=0.003), oppositionality (P=0.012), anxiousness (P=0.030), and self-harm (P=0.042) subscales of the DAPPs (see also Table 2).
On the Apathy Scale, 47% of the patients with acromegaly (odds ratio 3.3) had a score of 14 or more, indicative for the presence of clinically significant apathy, whereas 35% of the patients (odds ratio 2.0) had a score of 14 or more on the Irritability Scale, indicative for the presence of clinically significant irritability. On the HADS, 19% of the patients with cured acromegaly (odds ratio 2.1) scored greater than 13, indicative for the presence of clinically relevant depression or anxiety. There were significantly more patients than controls with clinically relevant scores on the Apathy Scale (P=0.001) but not on the other questionnaires.
The data on cognitive function are included as a supplemental table (Supplemental Table 1). There were a few significant differences between patients and controls in cognitive functioning. Patients with long-term cure of acromegaly scored significantly worse on only one verbal memory test, in which they remembered fewer words than controls in two of three trials (P=0.017 and P=0.012). Furthermore, patients performed worse on all aspects of a verbal fluency test (P=0.020).

Patients treated for NFMA versus their controls
Patients treated for NFMA scored worse only on the Apathy scale (P=0.001) and on the depression subscale of the HADS compared with their matched controls (P<0.001). On the DAPPs, NFMA patients scored worse on the trait affective lability (P=0.011), compared with controls (Table 3).
On the apathy scale, 40% of the NFMA patients (odds ratio 2.4) scored 14 or more and 27% of the patients (odds ratio 1.8) scored 14 or more on the Irritability Scale. Twenty-five percent of the patients (odds ratio 4.4) scored greater than 13 on the HADS. There were significantly more patients than controls with a clinically relevant score on the Apathy Scale and the HADS (P=0.034 and P=0.005, respectively).
The data on cognitive function are included as a supplemental table (Supplemental Table 2). There were hardly any differences between patients and controls in tests of cognitive function. Patients treated for NFMA scored better on the MMSE (P=0.013) but could remember fewer words on one of three trials measuring verbal memory (P=0.043). Furthermore, patients made more errors on one of two trials of the Trail-Making Test (P=0.007).

Table 2 Psychopathology and personality traits in patients with long term cure of acromegaly and their matched controls

	Acromgaly (n=68)	Matched controls (n=68)	P-value
Apathy Scale			
Total score	13.8 (6.1)	10.5 (4.8)	**0.001**
Score ≥14, n(%)	32 (47%)	14 (21%)	**0.001**
Irritability Scale			
Total score	12.7 (7.7)	9.5 (5.7)	**0.006**
Score ≥14, n(%)	24 (35%)	14 (21%)	0.056
HADS			
Anxiety	5.0 (3.7)	3.8 (3.1)	**0.031**
Depression	4.3 (4.2)	2.4 (2.8)	**0.003**
Score >13, n(%)	13 (19%)	7 (10%)	0.146
MASQ-30			
Negative Affect	16.6 (6.0)	15.1 (5.1)	0.126
Positive Affect	28.4 (8.8)	30.6 (8.2)	0.089
Somatic Arousal	14.6 (5.4)	12.9 (4.3)	**0.042**
DAPP			
Submissiveness	17.1 (6.2)	15.8 (5.0)	0.160
Cognitive distortion	9.9 (3.8)	8.8 (2.7)	0.055
Identity problems	11.0 (4.9)	9.8 (4.1)	0.128
Affective lability	19.2 (6.5)	16.0 (5.8)	**0.003**
Stimulus seeking	13.9 (4.0)	14.9 (5.0)	0.218
Compulsivity	22.3 (6.8)	21.8 (6.6)	0.653
Restricted expression	20.5 (6.3)	20.1 (5.7)	0.680
Callousness	16.5 (5.4)	16.0 (5.2)	0.558
Oppositionality	22.2 (7.4)	19.2 (6.4)	**0.012**
Intimacy problems	20.2 (7.4)	18.2 (5.6)	0.084
Rejection	18.9 (6.0)	18.7 (5.9)	0.776
Anxiousness	14.0 (5.3)	12.2 (4.3)	**0.030**
Conduct problems	9.8 (2.5)	9.6 (2.7)	0.616
Suspiciousness	11.2 (3.8)	12.1 (4.7)	0.206
Social avoidance	12.1 (5.3)	11.5 (4.5)	0.455
Narcissism	15.5 (5.8)	14.6 (4.9)	0.306
Insecure attachment	13.1 (6.0)	13.0 (5.6)	0.940
Self-harm	7.6 (3.8)	6.6 (2.0)	**0.042**

Data are mean (SD), unless otherwise mentioned

Supplementary Table 1 Cognitive outcomes: patients cured from acromegaly *vs* matched controls

		Acromegaly (n=68)	Matched Controls (n=68)	P-value
Global cognitive function				
MMSE	Score	28.3 (1.7)	28.2 (1.8)	0.722
Memory				
Wechsler Memory Scale	Memory Quotient	112.7 (17.2)	113.7 (15.8)	0.694
	Information	5.8 (0.4)	5.9 (0.3)	0.618
	Orientation	4.9 (0.3)	4.9 (0.3)	1.00
	Concentration	7.4 (1.7)	7.2 (1.8)	0.466
	Logical memory	6.8 (4.0)	6.8 (3.0)	
	Digit span	9.6 (1.9)	9.9 (1.9)	0.350
	Visual memory	8.6 (2.8)	8.5 (3.3)	0.744
	Associative learning	15.0 (3.6)	16.2 (2.8)	**0.017**
Verbal Learning Test of Rey	Imprinting, total	5.1 (1.9)	5.2 (2.2)	0.608
	Immediate, total	9.0 (2.6)	9.8 (2.5)	**0.027**
	Delayed, total	6.6 (3.1)	7.7 (3.2)	**0.012**
Rey Complex Figure test	Immediate	17.8 (5.4)	18.3 (6.9)	0.602
	Delayed	17.6 (5.5)	17.8 (7.0)	0.887
Executive functioning				
Trail making test	Trail A, time	0.4 (0.3)	0.4 (0.2)	0.537
	Trail A, errors	0.1 (0.4)	0.2 (0.4)	0.621
	Trail B , time	1.3 (0.8)	1.2 (0.9)	0.625
	Trail B, errors	0.6 (1.7)	0.8 (2.4)	0.649
Stroop color-word test	Interference, total	38.1 (10.0)	40.1 (10.0)	0.251
	Interference, mistakes	1.4 (5.7)	0.3 (0.7)	0.105
Letter-digit substitution test	# correct	31.2 (7.7)	31.7 (7.7)	0.657
	# errors	0.1 (0.3)	0.6 (3.9)	0.305
Digit-deletion test	# correct	376.1 (89.0)	395.0 (85.5)	0.188
	# missed	4.7 (4.2)	4.5 (5.5)	0.766
Figure Fluency	# patterns	58.0 (24.0)	57.6 (22.3)	0.906
	% repeats	11.3 (12.5)	8.3 (9.0)	0.120
	% errors	18.4 (15.2)	17.7 (14.8)	0.751
FAS	# correct	32.0 (13.3)	37.3 (13.9)	**0.019**
	% repeats	1.1 (1.9)	2.1 (3.1)	**0.015**
	% errors	4.0 (5.1)	1.7 (3.0)	**0.002**
Groninger Intelligence test	Synonyms score	4.5 (2.0)	4.9 (1.8)	0.132

Data are mean (SD)

Table 3 Psychopathology and personality traits in patients treated for NFMA and their matched controls

	NFMA patients (n=60)	Matched controls (n=60)	P-value
Apathy Scale			
Total score	13.1 (5.0)	10.4 (3.7)	**0.001**
Score ≥14, n(%)	24 (40%)	13 (22%)	**0.034**
Irritability Scale			
Total score	9.9 (5.7)	8.5 (5.3)	0.175
Score ≥14, n(%)	16 (27%)	10 (17%)	0.200
HADS			
Anxiety	4.5 (3.6)	3.6 (3.1)	0.131
Depression	4.1 (3.9)	1.9 (2.2)	**0.000**
Score >13, n(%)	15 (25%)	4 (7%)	**0.005**
MASQ-30			
Negative Affect	15.5 (5.7)	15.1 (5.6)	0.739
Positive Affect	29.6 (8.5)	30.5 (8.2)	0.562
Somatic Arousal	14.7 (5.2)	14.3 (4.8)	0.715
DAPP			
Submissiveness	16.7 (5.8)	16.9 (6.2)	0.832
Cognitive distortion	9.6 (4.0)	9.9 (4.8)	0.647
Identity problems	10.2 (4.9)	9.3 (4.3)	0.310
Affective lability	18.3 (5.7)	15.7 (5.7)	**0.011**
Stimulus seeking	14.6 (4.7)	14.7 (5.4)	0.861
Compulsivity	21.9 (6.8)	21.0 (5.8)	0.441
Restricted expression	21.6 (4.6)	20.5 (5.6)	0.227
Callousness	16.6 (4.6)	15.8 (4.3)	0.369
Oppositionality	20.6 (6.7)	19.2 (6.1)	0.242
Intimacy problems	20.0 (6.5)	20.3 (6.2)	0.810
Rejection	19.0 (11.1)	17.2 (5.7)	0.258
Anxiousness	12.8 (4.6)	12.3 (4.8)	0.542
Conduct problems	9.6 (2.7)	9.4 (2.3)	0.765
Suspiciousness	10.9 (3.4)	11.2 (4.0)	0.590
Social avoidance	11.1 (3.9)	10.3 (3.9)	0.232
Narcissism	15.5 (5.0)	14.7 (5.0)	0.378
Insecure attachment	12.9 (5.1)	12.6 (5.3)	0.827
Self-harm	6.9 (2.4)	6.4 (1.7)	0.199

Data are mean (SD), unless otherwise mentioned

Comparison of Z-scores between patients cured from acromegaly and patients treated for NFMA

Patients with long-term cure of acromegaly had higher scores on the negative affect subscale (P=0.05) and the somatic arousal subscale (P=0.009) of the HADS compared with treated NFMA patients. Furthermore, in comparison with NFMA

Supplementary Table 2 Cognitive outcomes: patients cured from NFMA *vs* matched controls

		NFMA (n=60)	Matched Controls (n=60)	P-value
Global cognitive function				
MMSE	Score	28.9 (1.1)	28.3 (.8)	**0.013**
Memory				
Wechsler Memory Scale	Memory Quotient	119.0 (16.7)	119.2 (14.2)	0.999
	Information	5.9 (0.3)	5.9 (0.3)	0.721
	Orientation	4.9 (0.3)	4.9 (0.2)	0.788
	Concentration	7.6 (1.8)	7.5 (1.4)	0.812
	Logical memory	7.4 (3.2)	7.5 (2.7)	
	Digit span	10.1 (1.6)	10.0 (1.6)	0.818
	Visual memory	8.9 (3.4)	8.7 (3.4)	0.686
	Associative learning	15.8 (2.9)	16.4 (3.2)	0.250
Verbal Learning Test of Rey	Imprinting, total	5.1 (1.8)	5.3 (1.9)	0.546
	Immediate, total	9.1 (2.9)	9.8 (2.1)	0.122
	Delayed, total	6.6 (3.4)	7.8 (2.8)	**0.043**
Rey Complex Figure test	Immediate	19.5 (6.8)	19.5 (6.1)	0.889
	Delayed	19.3 (6.4)	19.3 (6.3)	0.902
Executive functioning				
Trail making test	Trail A, time	0.6 (0.4)	0.5 (0.4)	0.109
	Trail A, errors	0.3 (0.5)	0.1 (0.3)	**0.007**
	Trail B , time	1.5 (0.7)	1.3 (0.7)	0.072
	Trail B, errors	0.6 (1.3)	0.5 (0.9)	0.641
Stroop color-word test	Interference, total	36.0 (8.4)	37.2 (8.0)	0.407
	Interference, mistakes	0.2 (0.4)	0.2 (0.5)	0.953
Letter-digit substitution test	# correct	30.7 (8.3)	31.1 (7.0)	0.721
	# errors	0.0 (0.2)	0.1 (0.4)	0.126
Digit-deletion test	# correct	358.4 (77.9)	382.2 (74.9)	0.054
	# missed	3.8 (4.2)	4.7 (4.6)	0.222
Figure Fluency	# patterns	48.1 (21.3)	54.6 (21.9)	0.083
	% repeats	8.9 (8.8)	6.6 (6.3)	0.107
	% errors	20.3 (11.3)	22.2 (15.4)	0.376
FAS	# correct	33.4 (12.9)	32.7 (11.4)	0.779
	% repeats	1.1 (2.0)	1.1 (2.0)	0.619
	% errors	2.2 (5.7)	1.8 (3.0)	0.873
Groninger Intelligence test	Synonyms score	5.2 (1.9)	4.9 (1.8)	0.395

Data are mean (SD)

patients, acromegaly patients scored worse on the submissiveness (P=0.049), cognitive distortion (P=0.001), identity problems (P=0.036), affective lability (P=0.044), oppositionality (P=0.025), anxiousness (P=0.005), and self-harm (P=0.008) subscales of the DAPPs. This is depicted in Figure 1 and Figure 2.
Patients with long-term cure of acromegaly scored worse on two aspects of executive functioning tests measuring attention, compared with NFMA patients, on which they worked more slowly (P=0.015) and made more mistakes (P=0.042). The memory tests were not different between the patient groups. The data on cognitive function are included as a supplemental table (Supplemental Table 3).

Comparison of psychopathology of patients with long-term cure of acromegaly and patients with NFMA by Z-scores, calculated for each patient group by comparison with their own matched control groups (i.e. Z-score of 0.0).

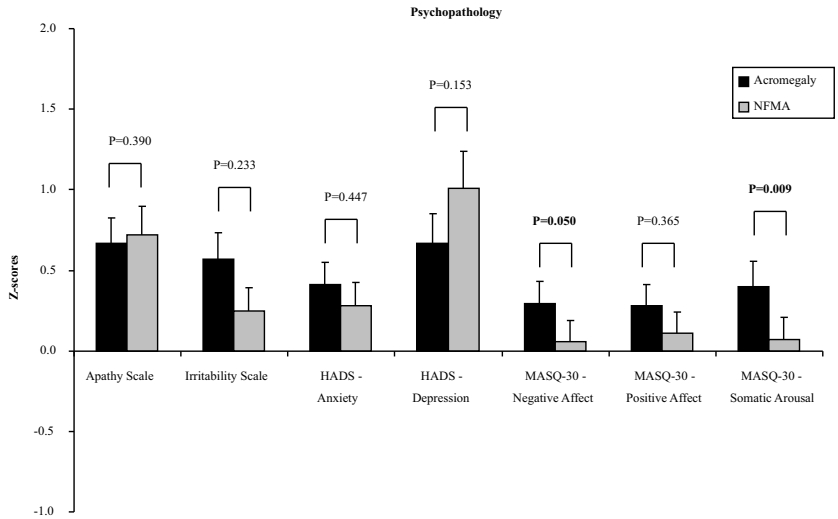

Figure 1: *Z-scores of patients cured of acromegaly and patients treated for NFMA, calculated for each patient group by comparison with their own matched control groups. Z-scores with standard errors are given in this figure. On the negative affect subscale and somatic arousal subscale of the MASQ-30 patients with long-term cured acromegaly scored worse when compared with patients with treated NFMA.*

Comparison of personality of patients treated for acromegaly and patients treated for NFMA by Z-scores, calculated for each patient group by comparison with their own matched control groups (i.e. Z-score of 0.0).

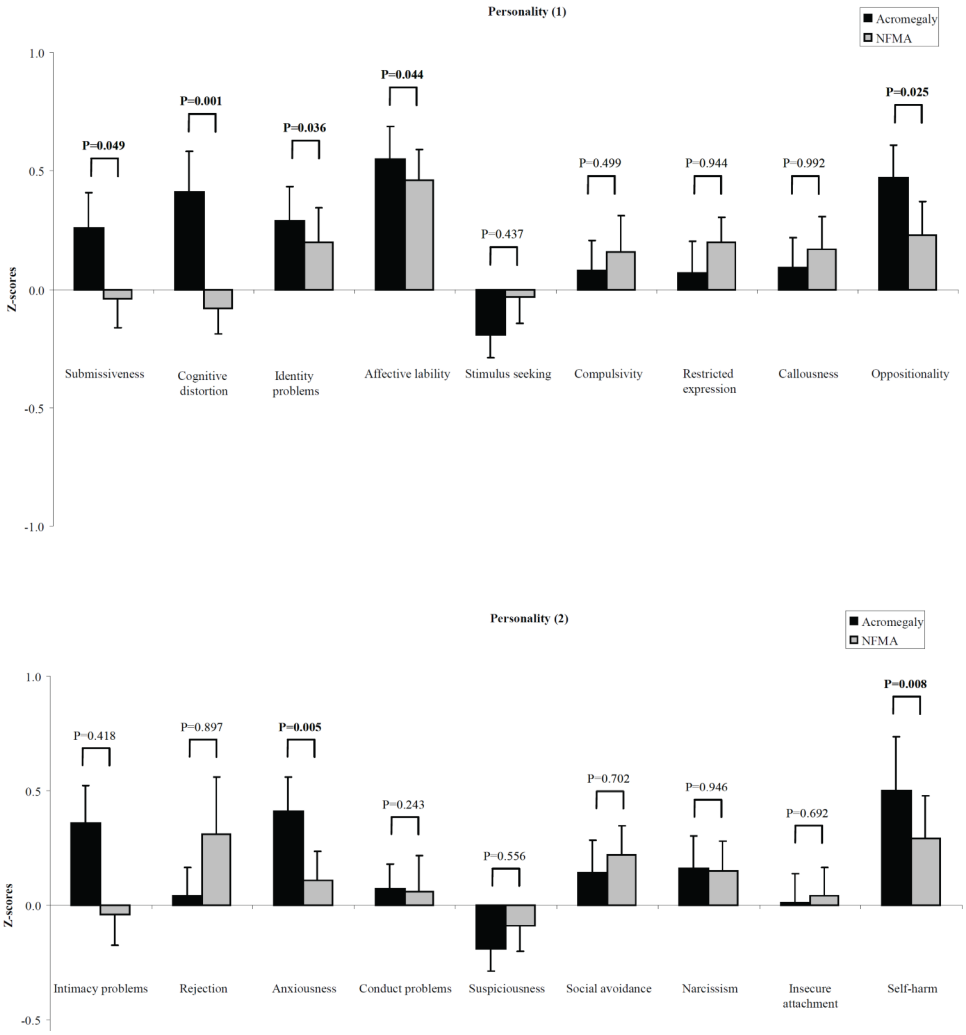

Figure 2: *Z-scores of patients cured of acromegaly and patients treated for NFMA, calculated for each patient group by comparison with their own matched control groups. Z-scores with standard errors are given in this figure. Patients with long-term cured acromegaly scored worse on the DAPP subscales submissiveness, cognitive distortion, identity problems, affective lability, oppositionality, anxiousness, and self-harm when compared with patients with treated NFMA.*

Supplementary Table 3. Cognitive function: comparison between patients with acromegaly and patients with NFMA by Z-scores, calculated for each patient group by comparison with their own matched controls

		Z-scores acromegaly (n=68)	Z-scores NFMA (n=60)	P-value
Global				
MMSE	Score	0.06 (-0.2 to 0.3)	0.35 (0.2 – 0.5)	0.236
Memory				
Wechsler Memory Scale	Memory Quotient	-0.06 (-0.3 to 0.2)	-0.01 (-0.3 to 0.3)	0.446
	Information	-0.09 (-0.4 to 0.2)	-0.04 (-0.4 to 0.3)	0.915
	Orientation	0.00 (-0.2 to 0.2)	-0.05 (-0.3 to 0.2)	0.794
	Concentration	0.11 (-0.1 to 0.3)	0.05 (-0.2 to 0.4)	0.652
	Logical memory	0.00 (-0.3 to 0.3)	-0.06 (-0.3 to 0.3)	0.828
	Digit span	-0.15 (-0.4 to 0.1)	0.04 (-0.2 to 0.3)	0.511
	Visual memory	0.05 (-0.2 to 0.2)	0.05 (-0.2 to 0.3)	0.417
	Associative learning	-0.41 (-0.7 to 0.1)	-0.19 (-0.4 to 0.1)	0.117
Verbal Learning Test of Rey	Imprinting, total	-0.07 (-0.3 to 0.1)	-0.11 (-0.4 to 0.2)	0.411
	Immediate, total	-0.34 (-0.6 to -0.1)	-0.34 (-0.7 to 0.1)	0.145
	Delayed, total	-0.36 (-0.6 to -0.1)	-0.41 (-0.7 to -0.1)	0.092
Rey Complex Figure test	Immediate	-0.07 (-0.3 to 0.1)	0.01 (-0.2 to 0.3)	0.051
	Delayed	-0.02 (-0.2 to 0.2)	0.00 (-0.2 to 0.3)	0.243
Executive function				
Trail making test	Trail A, time	0.09 (-0.2 to 0.4)	0.28 (0.0 – 0.5)	0.967
	Trail A, errors	-0.09 (-0.3 to 0.2)	0.75 (0.3 – 1.2)	0.406
	Trail B , time	0.07 (-0.2 to 0.3)	0.31 (0.0 – 0.6)	0.831
	Trail B, errors	-0.07 (-0.2 to 0.1)	0.11 (-0.3 to 0.5)	0.824
Stroop color-word test	Interference, total	-0.20 (-0.4 to 0.0)	-0.15 (-0.4 to 0.2)	0.345
	Interference, mistakes	1.55 (-0.3 to 3.5)	0.00 (-0.2 to 0.2)	0.355
Letter-digit substitution test	# correct	-0.07 (-0.3 to 0.2)	-0.06 (-0.3 to 0.3)	**0.018**
	# errors	-0.14 (-0.2 to -0.1)	-0.22 (-0.3 to -0.1)	0.325
Digit-deletion test	# correct	-0.22 (-0.5 to 0.0)	-0.32 (-0.6 to 0.0)	0.229
	# missed	0.05 (-0.1 to 0.2)	-0.19 (-0.4 to 0.0)	**0.042**
Figure Fluency	# patterns	0.02 (-0.2 to 0.3)	-0.30 (-0.5 to 0.0)	0.094
	% repeats	0.33 (0.0 – 0.7)	0.37 (0.0 – 0.6)	0.828
	% errors	0.05 (-0.2 to 0.3)	-0.13 (-0.3 to 0.0)	0.258
FAS	# correct	-0.38 (-0.6 to -0.1)	0.06 (-0.2 to 0.4)	0.148
	% repeats	-0.32 (-0.5 to -0.2)	0.03 (-0.2 to 0.3)	0.610
	% errors	0.77 (0.3 – 1.1)	0.14 (-0.4 to 0.4)	0.194
Groninger Intelligence test	Synonyms score	-0.22 (-0.5 to 0.0)	0.17 (0.0 – 0.5)	0.347

Data are Z-scores mean (95% CI)

Factors associated with psychopathology and personality traits in patients with cured acromegaly

Stepwise linear regression analysis was performed using the absolute test scores of the patients with long-term cure of acromegaly as dependent variables and pre-surgical GH level, pre-surgical IGF-I SD value, rhGH replacement therapy, somatostatin therapy, hypopituitarism, additional radiotherapy, duration of active disease, and duration of remission as independent variables.

The negative affect subscale of the MASQ-30 was negatively associated with hypopituitarism (β=-0.380, P=0.011), with hypopituitarism being associated with lower scores. The positive affect subscale of the MASQ-30 was negatively associated with radiotherapy (β=-0.348, P=0.022), which indicates that radiotherapy is associated with lower scores. However, only a small percentage of the patients received radiotherapy (22%, n=15), which makes it difficult to draw solid conclusions on the association between our parameters of interest and radiotherapy. Furthermore, the subscales compulsivity of the DAPPs (β=-0.334, P=0.027), restricted expression (β=-0.336, P=0.026), and insecure attachment (β=-0.307, P=0.043) were all negatively associated with rhGH replacement therapy, which means that patients who receive rhGH have a tendency to score lower on these subscales. The subscale oppositionality was positively associated with pre-surgical IGF-I SD value (β=0.323, P=0.033), which indicates that higher pre-surgical IGF-I SD values are associated with higher scores on oppositionality. The rejection subscale was negatively associated with pre-surgical GH level (β=-0.333, P=0.027), with higher preoperative GH levels being associated with a lower score. Anxiousness was negatively associated with duration of remission (β=-0.311,P=0.040), with longer duration of remission being associated with lower anxiousness.

Discussion

This study demonstrates that patients with long-term cure of acromegaly suffer from increased psychopathology and maladaptive personality traits, but hardly from increased cognitive dysfunction, compared with matched controls. Patients with long-term cure of acromegaly also showed more psychopathology, and especially more maladaptive personality traits, compared with patients treated for NFMA. These observations indicate that the increased psychopathology and maladaptive personality traits observed in patients with long-term cure of acromegaly are not merely caused by pituitary adenomas per se and/or their treatment, but rather by previous GH excess.

A direct comparison of parameters of interest between patients with long-term

cure of acromegaly and patients treated for NFMA is confounded by relevant differences in other clinical characteristics. Therefore, we included matched control subjects for each patient group. We calculated Z-scores for each patient group in comparison with their own matched controls. Subsequently we compared these Z-scores to detect possible differences between patients with acromegaly and NFMA patients. By using these Z-scores, we have carefully corrected for the differences in clinical characteristics between both groups of patients. We have used this approach for similar problems in the comparison of patients with Cushing's disease *versus* patients with NFMA (25, 26).

Table 4 summarizes the previous studies on psychopathology in patients with acromegaly. Previous studies on psychopathology in patients with active acromegaly reported affective disorders, fatigue, and loss of drive causing irritability and impatience (3). Most patients cured of acromegaly notice an increase in physical well-being (6), but they still have a high prevalence of psychological distress, especially anxiety disorders and major depression (27, 28), although another study found only increased prevalence of affective disorders (29). Limitations of those studies are the limited number of included patients, and heterogeneous clinical characteristics. Moreover, the effects of long-term cure of acromegaly have not been studied in detail.

Several previous studies assessed the effects of acromegaly on personality (Table 4). Patients with active acromegaly were characterized by industriousness, conscientiousness, and compulsiveness and sometimes lack of self-confidence (3). Furthermore, in patients with active acromegaly, a high need for sociability, high self-assuredness, and industry have been reported (4). After treatment, patients with acromegaly show a pattern of increased anxiety-related personality traits with reduced impulsivity and novelty-seeking behavior (30). Thus, those previous studies indicate that maladaptive personality traits are present in active and treated acromegaly patients.

Our study extends these results by indicating that maladaptive personality traits remain present after very long-term cure of acromegaly. Our study differs in several respects from previous studies. First, the number of patients included is relatively large in the present study compared with earlier studies. Second, the duration of cure was very long in our study compared with previous studies. Third, we compared patients with long-term cure of acromegaly both with matched controls and with patients previously treated for NFMA. From the current study, in addition to the studies summarized in Table 4, the notion emerges that patients with *active* acromegaly suffer from increased prevalence of psychopathology and maladaptive personality traits, and that long-term treatment of acromegaly results in some, but not complete, recovery of these parameters.

Patients with long-term cure of Cushing's disease suffer from impaired cognitive

functioning (25). This is in contrast to the current observations in patients with long-term cure of acromegaly. We speculate that these differences in cognitive function between patients with long-term cure of acromegaly and patients with long-term cure of Cushing's disease are explained by glucocorticoid specific irreversible effects on the central nervous system on structures involved in cognitive function, which are apparently not affected by previous GH and IGF-I excess.

In the present study, the outcomes of the questionnaires in patients with long-term cure of acromegaly were still well within the normal reference ranges of -2 SD and +2 SD (Figs. 1 and 2). Anecdotal reports have documented patients with pituitary disease and an apathy syndrome who had been incorrectly diagnosed as major depression and who had been treated accordingly with antidepressants for a long time (31). Our own subjective experiences in routine clinical practice suggest that there are subtle differences between the personalities of patients cured from acromegaly and those of patients with other pituitary diseases. However, clinical endocrinologists are not trained to detect subtle manifestations of psychopathology and maladaptive personality traits. We speculate that the results of our study confirm the clinical impression that patients cured from acromegaly have different and more serious complaints than patients with NFMA, even though patients treated for NFMA have a higher incidence of hypopituitarism.

In summary, patients with long-term cure of acromegaly have a high prevalence of psychopathology, compared with matched controls. Furthermore, patients with long-term cure of acromegaly have a greater degree of maladaptive personality traits, compared with both matched controls and patients treated for NFMA. These results suggest irreversible effects of previous GH excess on the brain, rather than effect of pituitary adenomas and/or their treatment in general.

Table 4 Overview of studies on psychopathology and personality in patients with acromegaly

Author, year	Number of subjects	Gender (m/f)	Age (yr), mean ± sd	Active/treated	Duration of disease control	Methods	Outcomes
Richert, 1983 (3)	Acromegaly: 20	4/16	uk	Controlled (10) Surgery (10) RT (0) SMS (0) Active (10)	6-9 months following transsphenoidal adenomectomy	H-W test, Luria test, Ravens test, D2-A test	Premorbid personality is very similar in all acromegalic patients. Psychopathological symptoms include fatigue and loss of drive. Postoperative: loss of drive and mental disorders improve. When GH is not normalized: more depression and anxiety.
Sablowski, 1986 (4)	Acromegaly: 9 Cushing's disease: 9 Prolactinoma: 6 CNS disease: 24	uk	uk	Active (9), measured again 1 week after surgery	Measured 2-4 days after hospitalisation and again 1 week post-surgery	FPI, Giessen test, STAI	Tendency to higher scores of trait-anxiety in adenoma patients compared to controls. Compared to other pituitary tumor patients; acromegaly patients show relatively little anxiety and depression, but show a high need for sociability, high self-assuredness, and industry.
Flitsch, 2000 (6)	Acromegaly:18 Cushing's disease: 19 NFMA: 11	12/6	46 ± 7	Active (18), measured again 6-8 months after surgery	Re-examined 6-8 months after surgery	Semi-structured interview, FPI, STAI, PFT, Bf-S, GBB	Fatigue and loss of energy were the most reported problems in acromegaly. After surgery, most patients noticed an increase in physical well-being.
Sonino, 2004 (27)	Acromegaly: 10 Other endocrine: 136	uk	39 ± 13 (all patients)	Controlled (10) Surgery (uk) RT (uk) SMS (uk)	Cured disease or in remission for at least 6 months	SCI DSM-IV, DCPR, PSI, MOS	81% of the total sample presented at least one psychiatric or psychological disorder. High prevalence of psychological distress in long-term follow-up endocrine patients. Most frequent findings: anxiety disorders and major depression.
Sonino, 2007 (28)	Acromegaly: 10 Other pituitary: 76 Non-pituitary: 60	uk	39 ± 12 (all patients)	Controlled (10) Surgery (4) RT (uk) SMS (7)	Cured disease or in remission for > 9 months < 3 years	SCI-DSM-IV, DCPR, PSI, MOS	Endocrine patients report more stressful life circumstances, psychological distress, abnormal illness behaviour and pain than controls. Endocrine patients show more psychopathology, psychological distress and impaired QoL after curation or remission when compared to controls.
Tanriverdi, 2008	Acromegaly: 18	7/11	40 ± 11	Active (18)	-	P300 auditory event	Mean P300 amplitude in acromegaly patients

(7)	GH deficiency: 19 Matched controls: 16					related potentials (ERPs)	significantly lower than in normal controls and GH deficiency patients. Negative correlation between IGF-I levels and P300 amplitudes. P300 amplitude is related to decision making and memory processing, which is lower in patients with acromegaly.
Sievers, 2009 (30)	Acromegaly: 70 NFMA: 58 Normal controls: 140	31/39	55 ± 11	Controlled (46) Surgery (65) RT (19) SMS (25) Active (24)	uk	EPQ-RK, TPQ	Compared to healthy controls, patients with acromegaly show a pattern of increased anxiety-related personality traits. Acromegaly seemed to be associated with reduced impulsivity and novelty-seeking behaviour.
Sievers, 2009 (29)	Acromegaly: 81 Controls with chronic somatic disorder: 3281 Controls without somatic disorder: 430	38/43	55	Controlled (47) Surgery (73) RT (20) Medical treatment (44) Active (34)	Mean time after surgery 10 yr	DIA-X/M-CIDI	Patients with acromegaly show increased prevalence of affective disorders (major depression and dysthymia), but not anxiety disorders.
Present study	Acromegaly: 68 Matched controls: 68 NFMA: 60 Matched controls: 60	35/33	59 ± 11	Controlled (68) Surgery (68) RT (15) SMS (11)	Duration of remission 13 ± 8 yr	Apathy Scale, Irritability Scale, HADS, MASQ-30, DAPP, MMSE, WMS, VLTR, RCFT, TMT, SCWT, LDST, DDT, FFT, FAS, GIT-synonyms	Patients with long-term cure of acromegaly show a higher prevalence of psychopathology and more maladaptive personality traits, but not more cognitive dysfunction compared to both matched controls and treated NFMA patients.

uk: unknown, RT: radiotherapy, SMS: somatostatin, H-W test: Hamburg-Wechsler test, D2-A test: d2-aufmerksamkeitstest, FPI: Freiburger personality inventory, STAI: State-trait-anxiety inventory, ROCFT: Rey-Osterrieth complex figure, COWAT: Controlled oral world association test, WMS: Wechsler memory scale, WRMT: Warrington recognition memory test, NART: National adult reading test, AVLT: Auditory verbal learning test, RMTF: Recognition memory test for faces, SNST: Stroop neuropsychological screening test, TMT: Trail making test, AMI: Autobiographical memory inventory, RMT: Recognition memory test, WAIS: Wechsler adult intelligence scale, NHP: Nottingham health profile, EPI: Eysenck personality inventory, PFT: Rosenzweig Picture frustration test, Bf-S: Befindlichkeitsskala, GBB: Giessener beschwerdebogen, RFC: Rey figure copy, SCOLP: Speed and capacity of language processing, EMQ: Everyday memory questionnaire, HADS: Hospital anxiety and depression questionnaire, GHQ: General health questionnaire, SF36: Short form health status questionnaire, GWBS: General well being schedule, SCI DSM-IV : Structural clinical interview for DSM-IV, DCPR: Diagnostic criteria for psychosomatic research, PSI: Psychosocial index, MOS: Medical outcomes study short form General health survey, EPQ-RK: Eysenck and cloninger personality questionnaire, TPQ: Tridimensional personality questionnaire, DIA-X/M-CIDI: Composite international diagnostic interview for DSM-IV, MASQ-30: Mood and anxiety symptoms questionnaire, DAPP: Dimensional assessment of personality pathology, MMSE: Mini mental state examination, VLTR: Verbal learning test of rey, RCFT: Rey complex figure test, SCWT: Stroop color word test, LDST: Letter-digit substitution test, DDT: Digit-deletion test, FFT: Figure fluency test, GIT: Groninger Intelligence test

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Chapter 9

General discussion and summary

Contents

1. Introduction

In the present thesis, we explored the long-term consequences of pituitary diseases from a psychological perspective. Pituitary and adrenal adenomas can be treated quite adequately from a medical perspective, but these patients suffer from impaired quality of life (QoL) despite long-term remission or cure. This decreased QoL is assumed to originate mostly from physical complaints, but psychological problems might also contribute.

2. Illness perceptions

Although decreased QoL may originate from persisting limitations due to irreversible effects of previous excessive hormone exposure, an alternative hypothesis is that the psychological impact of suffering from this disease reduces QoL. The aim of the study described in **Chapter 2** was to explore the illness perceptions of patients after long-term remission of Cushing's syndrome. This is the first time that illness perceptions are addressed in endocrine diseases in general. We used several validated QoL questionnaires and the Illness Perception Questionnaire Revised to assess QoL and illness perceptions. The results indicate that affected illness perceptions and reduced QoL parameters are strongly related. Moreover, patients after long-term remission of Cushing's syndrome reported more negative illness perceptions compared with several reference groups with acute and chronic conditions. In addition, patients with hydrocortisone dependency had stronger beliefs regarding the chronic nature and the cyclical nature of Cushing's syndrome than patients without hydrocortisone dependency. Furthermore, hypopituitarism was associated with the number of symptoms attributed to Cushing's syndrome, chronicity and fluctuations of the disease, and the perceived consequences of Cushing's syndrome. Therefore, hydrocortisone dependency and hypopituitarism both influence illness perceptions.

The perceptions of patients depend on information from different sources. Therefore, these illness perceptions do not necessarily represent the actual medical status of the disease. This might explain why patients in remission of Cushing's syndrome perceive their illness as chronic or cyclical and believe that psychological attributions might have caused Cushing's syndrome.

The current study also demonstrates that there is a strong relationship between illness perceptions and QoL. This has already been observed in multiple other medical conditions (1). This relationship is a relevant observation, since patients with long-term cure of Cushing's syndrome have persistent complaints reflected in impaired QoL (2-4). These complaints are often misunderstood and difficult to treat.

Therefore, awareness of how these patients perceive their disease and its consequences could lead to a better understanding of Cushing's syndrome and its long-term effects.

In **Chapter 3** we aimed to explore illness perceptions in patients after long-term biochemical control of acromegaly. We used several validated QoL questionnaires and the Illness Perception Questionnaire Revised to assess QoL and illness perceptions. The results indicated that patients with long-term remission of acromegaly have a good understanding of their disease, but they experience a lack of personal control and are not very likely to seek medical care. Interestingly, there are clear differences between illness perceptions in acromegaly and other diseases. For example, acromegalic patients reported more negative illness perceptions than patients with acute pain or vestibular schwannoma, but more positive illness perceptions than patients with chronic conditions, like chronic obstructive pulmonary disease. In addition, patients with long-term remission of acromegaly perceived impaired QoL. The illness perceptions in patients with acromegaly correlated strongly with QoL parameters, in accordance with our observations in patients with long-term cure of Cushing's disease and in other conditions (**Chapter 2**, (1)).
Patients in long-term remission of acromegaly reported somewhat more positive illness perceptions than patients after long-term remission of Cushing's syndrome. It is tempting to speculate that there are disease-specific characteristics in illness perceptions in addition to more general influences related to complaints or chronicity. Additional research is needed to see whether these findings can be extended to other endocrine diseases.
It is important for endocrinologists to explain to the patients what might have caused acromegaly, and ask the patient what their perceived cause of acromegaly is. The illness perceptions of patients, including those pertaining to the perceived cause of acromegaly, are based on various sources which indicates that illness perceptions do not necessarily represent the actual medical status or cause of acromegaly.
The current explorative study is important, since patients with acromegaly suffer from impaired QoL even after long-term remission (5-7). The somatic and psychological factors that contribute to decreased QoL are not well-known, but most likely include musculoskeletal complaints (5), pituitary insufficiency (8;9) and the perception of the patients of their disease.

In conclusion, there is a strong correlation between illness perceptions and decreased QoL in patients with long-term remission of Cushing's syndrome as well as in patients after long-term remission of acromegaly. Patients after long-term re-

mission of Cushing's syndrome reported more negative illness perceptions compared with various reference samples with acute and chronic diseases. Patients with long-term remission of acromegaly reported more negative illness perceptions than patients with acute illness, but more positive illness perceptions than patients with chronic diseases including Cushing's syndrome.

In the studies described above, the Common Sense Model of self-regulation (CSM) by Leventhal *et al.* was used as starting point to understand the relation between illness, illness perceptions, coping strategies, and outcome (10-13). Based on the performed studies described in this thesis and a recent meta-analytic review of the CSM (14), we postulate that the CSM should incorporate a new arm that represents QoL. The studies described in **Chapter 2** and **Chapter 3** show that illness perceptions and QoL are strongly correlated. We revised the existing CSM, which is depicted in Figure 1. We should note that further research is necessary to establish the correctness of the proposed addition of QoL in the CSM, and whether QoL is involved in the feedback loop of the CSM.

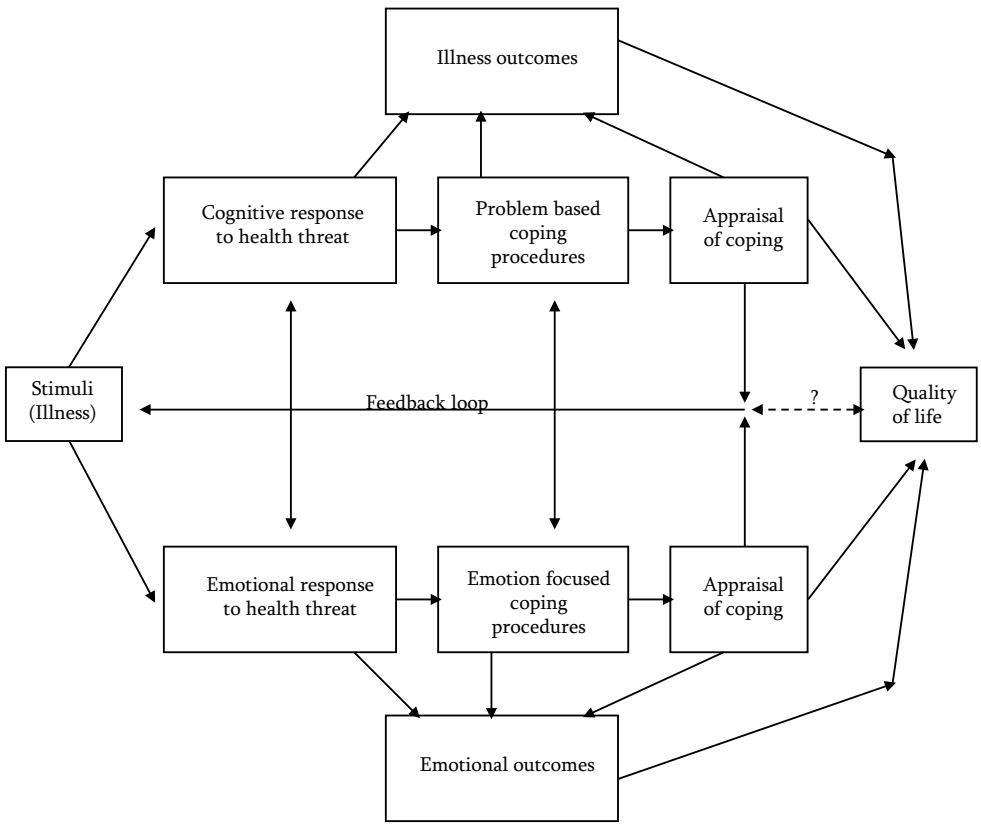

Figure 1. *The revised Common Sense Model, partially based on Hagger & Orbell (2003)*

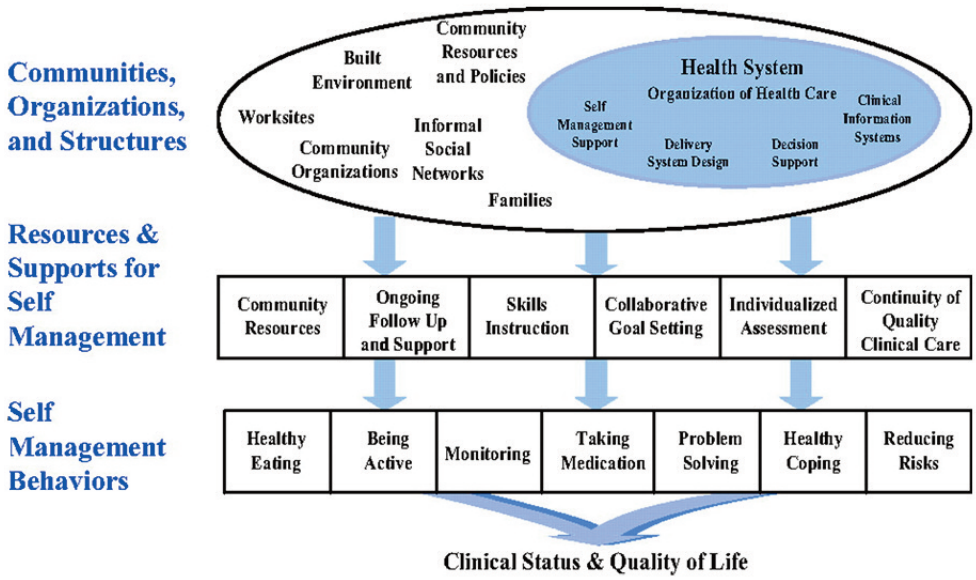

Figure 2. *Trilevel Model of Self-Management and Chronic Care, adapted from Fischer et al. (2007)*

In addition, the CSM does not encompass contextual factors. These contextual factors are, however, embedded in the Chronic Care Model (CCM) (15). The CCM incorporates self-management into a social context and characteristics of the healthcare system. Both the CSM and the CCM revolve around the central position of the patient in medical care for chronic illnesses. An important difference between the models is that the CCM focuses on beliefs about the target behavior, while the CSM includes beliefs about the illness. Therefore, Fischer *et al.* (16) developed the Trilevel Model of Self-Management and Chronic Care that ties together the CSM and the CCM (see Figure 2).

Based on this Trilevel Model and our findings, we strongly encourage the development of a self-management intervention for (treated) pituitary patients. This intervention should incorporate self-management (17) and should intervene in illness perceptions, which is a dynamic process. Another important aspect to take into account in this intervention is self-efficacy (18;19), which might also play a role in the willingness of patients to change their illness perceptions and/or coping strategies.

We believe that the proposed intervention will ultimately lead to a better QoL, since illness perceptions and QoL are closely related in pituitary diseases. The CSM implies that changing illness perceptions may lead to changes in relevant self-management behaviors. Previous studies have already shown that psycho-

education interventions can indeed change negative illness perceptions (13;20) and thereby self-management and, consequently, outcome (i.e. QoL).

3. Coping strategies

In **Chapter 4**, we aimed to investigate coping strategies of patients after treatment for pituitary adenomas. We used the Utrecht Coping Lijst to assess coping. The study demonstrated that patients after appropriate treatment for pituitary adenomas report less active coping, more avoidance coping and seek less social support compared with an a-select sample from the Dutch population. Compared with patients with chronic pain, patients treated for pituitary adenomas sought more social support. Patients after treatment for pituitary disease were also compared with patients in primary care psychology services. Patients with pituitary adenomas scored lower on avoiding, seeking social support, passive coping, and expressing emotions, but higher on active coping. This indicates that patients treated for pituitary adenomas report less effective coping strategies compared with the normal population, but apparently use more effective coping strategies than patients with chronic pain and patients in primary care psychology services. Furthermore, patients after treatment for Cushing's disease, acromegaly, and NFMA did not differ from each other with respect to coping strategies, besides the fact that patients with Cushing's disease sought more social support than patients treated for NFMA.
This is the first study that explored coping strategies in patients treated for Cushing's disease, acromegaly, or NFMA. We believe that information on coping strategies of these patients is important, since they suffer from chronic and multiple disabilities despite long term cure of their initial pituitary adenoma (2-5;21-25), which are often misunderstood and difficult to treat. Knowledge of the coping strategies can be used in designing an intervention based on e.g. cognitive behavioural therapy, self-management training, and information on the negative effects of the disease.

In conclusion, patients treated for Cushing's disease, acromegaly, or NFMA display different and less effective coping strategies compared with healthy controls. Compared with patients with chronic pain and patients receiving primary care psychology services, patients treated for pituitary adenomas report somewhat better coping strategies. Therefore, there is a need to develop, to apply and to evaluate coping skills training and self-management in patients with this condition.

4. Cognitive functioning

In **Chapter 5**, we aimed to assess cognitive function in patients after long-term remission of Cushing's disease. We used eleven cognitive tests to assess the entire spectrum of cognition. We compared patients after long-term remission of Cushing's disease with matched controls, and with patients after treatment for NFMA using Z-scores. This study demonstrated that cognitive function is impaired in patients despite long-term cure of Cushing's disease. These patients reported impairments in memory in daily life, which was confirmed by cognitive functioning tests. The performance was decreased in certain aspects of executive functioning and several memory tasks, compared with matched controls. These impairments were not merely related to pituitary disease in general, since these patients with long-term cure of Cushing's disease also revealed impaired cognitive function compared with patients previously treated for NFMA. These observations indicate irreversible effects of previous hypercortisolism on cognitive function and, thus, on the central nervous system.
Several clinical characteristics influenced outcome parameters. Hypopituitarism was associated with mildly impaired executive functioning. Hydrocortisone dependency and additional radiotherapy were negatively associated with memory and executive functioning, whereas the duration of remission positively influenced memory and executive functioning.
Prolonged glucocorticoid excess modifies neurotransmitter function and neuronal structure of the central nervous system (26;27). In rodents, chronic exposure to high levels of glucocorticoids impairs hippocampal long-term potentiation (28), and decreases hippocampal synaptic plasticity (29). In humans, endogenous active Cushing's disease is associated with cognitive impairment (27;30;31). The hippocampus is one of the most sensitive structures in the brain for glucocorticoids and is crucial in cognitive function (32). The persistent impairments in cognitive function in patients with previous Cushing's disease might be explained by irreversible effects of previous glucocorticoid excess on the central nervous system, especially the hippocampus. Additional studies, including functional MRI and postmortem analyses of the central nervous system, are required to evaluate the effects of previous glucocorticoid excess on brain areas of interest.

In **Chapter 8**, we described a cross-sectional study in which we assessed cognitive functioning in patients after long-term remission of acromegaly. We compared these patients with matched controls, and with patients after treatment for NFMA using Z-scores.
We found no differences in cognitive functioning between patients after long-term remission of acromegaly and matched controls or NFMA patients. However,

in contrast, patients with long-term cure of Cushing's disease suffered from impaired cognitive functioning (**Chapter 5**, (3)). We speculate that these differences in cognitive function between patients with long-term cure of acromegaly and patients with long-term cure of Cushing's disease are explained by glucocorticoid-specific, irreversible effects on the central nervous system on structures involved in cognitive function, which are apparently not affected by previous GH/IGF-I excess.

In summary, there are subtle impairments in cognitive function in patients during long-term follow up after cure of Cushing's disease compared with NFMA patients and matched controls. The greatest impairment was present in memory, although executive functioning was also affected. This impairment in cognitive function after treatment of Cushing's disease is not merely the result of pituitary disease in general and/or its treatment, but includes specific elements most likely caused by the irreversible effects of previous glucocorticoid excess on the central nervous system. However, there were no differences in cognitive functioning between patients after long-term remission of acromegaly and matched controls or NFMA patients. We postulate that previous GH/IGF-I excess does not cause irreversible effects on parts of the central nervous system important in cognitive functioning.

5. Prevalence of psychopathology

We analyzed the prevalence of psychopathology and maladaptive personality traits in patients after long-term remission of Cushing's disease in **Chapter 6**. We used several validated questionnaires to assess psychopathology, i.e. the Apathy Scale, Irritability Scale, Hospital Anxiety and Depression Scale, and the Mood and Anxiety Symptoms Questionnaire (short-form). We used the Dimensional Assessment of Personality Pathology (short-form) to evaluate personality traits. This study demonstrated that patients with long-term cure of Cushing's disease suffer from more psychopathology and maladaptive personality traits compared with matched controls. In addition, patients with long-term cure of Cushing's disease had significantly more psychopathology and maladaptive personality traits than patients previously treated for NFMA, indicating that the presence of psychopathology and maladaptive personality traits was not merely related to pituitary tumors and/or their treatment in general. Therefore, the long-term effects of cured Cushing's disease on psychopathology and personality traits are more likely to be the consequence of previous glucocorticoid excess. These observations point to irreversible effects of previous glucocorticoid excess on the central nervous system.
In **Chapter 7**, we reviewed the current literature on psychopathology and Cush-

ing's disease. Active Cushing's disease is associated with a high prevalence of psychopathology, mainly atypical depression. Treatments with glucocorticoid reducing or blocking agents can rapidly relief symptoms. After successful surgery, prevalence of psychopathology decreases, whereas mood and behavior do not seem to normalize. After long-term remission, patients with Cushing's disease still show decreased QoL and impaired cognitive function.

In **Chapter 8**, we described the prevalence of psychopathology and maladaptive personality traits –as well as cognitive functioning (see section IV. Cognitive functioning)– in patients after long-term remission of acromegaly. We used the same validated questionnaires as the study described in **Chapter 6**, i.e. the Apathy Scale, Irritability Scale, Hospital Anxiety and Depression Scale, and the Mood and Anxiety Symptoms Questionnaire (short-form). We used the Dimensional Assessment of Personality Pathology (short-form) to evaluate personality traits. The study demonstrated that patients with long-term cure of acromegaly suffer from an increased prevalence of psychopathology and maladaptive personality traits compared with matched controls. Patients with long-term cure of acromegaly also showed more psychopathology, and especially more maladaptive personality traits, compared with patients treated for NFMA. These observations indicate that the increased psychopathology and maladaptive personality traits observed in patients with long-term cure of acromegaly are not merely caused by pituitary adenomas per se and/or their treatment, but rather by previous GH excess. We speculate that the results of our study confirm the clinical impression that patients cured from acromegaly have different and more serious complaints than patients with NFMA, even though patients treated for NFMA have a higher incidence of hypopituitarism.

In summary, patients with long-term cure of Cushing's disease report a high prevalence of psychopathology, compared with both matched controls and patients previously treated for NFMA. Furthermore, patients with long-term cure of Cushing's disease have a greater degree of maladaptive personality traits. In addition, patients with long-term cure of acromegaly also have a high prevalence of psychopathology, compared with matched controls. Patients with long-term cure of acromegaly have a greater degree of maladaptive personality traits, both compared with matched controls and to patients treated for NFMA. The results suggest that these observations reflect irreversible effects of previous glucocorticoid or GH/IGF-I excess on the central nervous system rather than an effect of pituitary tumors and/or their treatment in general. Future studies should aim at further investigating if and how glucocorticoids and GH/IGF-I changes (subclinical) psychopathology.

6. Summary and concluding remarks

The present thesis describes the long-term psychological consequences of pituitary diseases. From the studies described in this thesis we can conclude that:

- Patients after long-term remission of Cushing's syndrome have more negative illness perceptions compared with patients with acute and chronic conditions.
- Patients after long-term remission of acromegaly have more negative illness perceptions than patients with acute conditions.
- Illness perceptions and QoL are strongly correlated in patients after long-term remission of Cushing's syndrome, as well as in patients after long-term remission of acromegaly.
- Patients treated for a (non)functioning pituitary adenoma display different and less effective coping strategies compared with healthy controls.
- Patients after long-term remission of Cushing's disease show subtle impairments in cognitive functioning compared with matched controls and NFMA patients.
- There were no differences in cognitive functioning between patients after long-term remission of acromegaly and matched controls or NFMA patients.
- Patients after long-term remission of Cushing's disease or acromegaly have a higher prevalence of psychopathology and maladaptive personality traits than both matched controls and NFMA patients.

Nowadays, pituitary adenomas can be appropriately treated, but patients continue to report impaired QoL despite long-term remission or cure.

In patients with Cushing's disease, Cushing's syndrome or acromegaly, doctors should be aware of subtle cognitive impairments and the increased prevalence of psychopathology and maladaptive personality traits after long-term remission. In addition, these patients use ineffective coping strategies and have negative illness perceptions that are not always correct. Patients are labeled 'cured', but still experience chronic and persisting impairments due to their pituitary disease. Doctors should consider informing patients better about the long-term consequences and act as a guide in this 'acceptance process' of the patient. In addition, a multidisciplinary team of endocrinologists, psychologists, and community health workers might also help patients in accepting and dealing with the consequences of their pituitary disease.

We strongly encourage the development of a self-management intervention, including coping skills training, for patients with pituitary diseases. This intervention might help these patients to cope with their impairments and change illness perceptions. We postulate that this approach might ultimately lead to a better QoL.

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Chapter 10

Nederlandse samenvatting

Inhoud

1. Inleiding

In dit proefschrift hebben we de lange termijn effecten van hypofysaire ziekten onderzocht vanuit een psychologisch perspectief. Hypofyse adenomen kunnen vanuit medisch perspectief goed worden behandeld. Toch behouden hypofyse patiënten een verminderde kwaliteit van leven terwijl zij al langdurig in remissie of genezen zijn. Er wordt verondersteld dat deze vermindering in kwaliteit van leven voornamelijk wordt veroorzaakt door lichamelijke klachten, maar psychische problemen kunnen hierbij ook een rol spelen.

2. Ziektepercepties

De verminderde kwaliteit van leven zou veroorzaakt kunnen worden door beperkingen ten gevolge van eerdere excessieve hormoonoverproductie. Een alternatieve hypothese is dat de psychische impact van het hebben van een hypofysaire ziekte zou kunnen leiden tot een verminderde kwaliteit van leven.
Het doel van de studie beschreven in Hoofdstuk 2 was om de ziektepercepties van patiënten in remissie van het syndroom van Cushing in kaart te brengen. Dit was de eerste keer dat ziektepercepties onderzocht werden in endocriene ziekten. We hebben hiervoor een aantal gevalideerde vragenlijsten gebruikt om de kwaliteit van leven te meten en de Illness Perception Questionnaire Revised (IPQ-R) om de ziektepercepties te onderzoeken. De resultaten laten zien dat ziektepercepties en kwaliteit van leven sterk met elkaar correleren. Bovendien rapporteren patiënten na langdurige remissie van het syndroom van Cushing meer negatieve ziektepercepties in vergelijking met een aantal referentie groepen met acute en chronische aandoeningen. Daarnaast hebben patiënten die hydrocortison afhankelijk zijn het idee dat hun ziekte chronischer en cyclischer van aard was dan patiënten die geen hydrocortison gebruiken. Hypofysaire uitval werd verder geassocieerd met een aantal symptomen die werden toegeschreven aan het syndroom van Cushing, de chroniciteit en schommelingen van de ziekte, en de waargenomen gevolgen van het syndroom van Cushing. We concluderen dat zowel hydrocortison afhankelijkheid als hypofysaire uitval van invloed zijn op de ziektepercepties van deze patiënten.
Omdat de percepties van patiënten afhankelijk zijn van informatie uit verschillende bronnen, is het niet noodzakelijkerwijs zo dat deze ziektepercepties de medische status van de ziekte representeren. Dit zou kunnen verklaren waarom patiënten in remissie van het syndroom van Cushing hun ziekte toch als chronisch of cyclisch beschouwen en denken dat een psychologische attributie het syndroom van Cushing zou hebben veroorzaakt.
De huidige studie toont ook aan dat er een sterke relatie is tussen ziektepercepties en kwaliteit van leven. Dit is reeds waargenomen in verschillende andere me-

dische aandoeningen. Deze relatie is relevant, aangezien patiënten na langdurige genezing van het syndroom van Cushing aanhoudende klachten hebben die gereflecteerd worden in een verminderde kwaliteit van leven. Deze klachten worden vaak niet goed begrepen en zijn moeilijk te behandelen. Het is daarom van belang dat artsen zich bewust zijn hoe deze patiënten hun ziekte en de gevolgen daarvan ervaren. Dit zal leiden tot een beter begrip van het syndroom van Cushing en de lange termijn effecten ervan.

In Hoofdstuk 3 hebben we ons gericht op de ziektepercepties van patiënten na biochemische controle van acromegalie. We hebben een aantal gevalideerde kwaliteit van leven vragenlijsten en de IPQ-R gebruikt om kwaliteit van leven en ziektepercepties te meten. De resultaten laten zien dat patiënten na langdurige remissie van acromegalie een goed begrip van hun ziekte hebben, maar een gebrek aan persoonlijke controle ervaren en niet snel om medische hulp vragen. Het is interessant dat er duidelijke verschillen in ziektepercepties waar te nemen zijn bij patiënten met acromegalie en andere ziekten. Acromegalie patiënten rapporteerden bijvoorbeeld meer negatieve ziektepercepties dan patiënten met acute pijn of vestibularis schwannoom, maar meer positieve ziektepercepties dan patiënten met chronische aandoeningen zoals COPD. Daarnaast ervaren patiënten in langdurige remissie van acromegalie een verminderde kwaliteit van leven. De ziektepercepties van acromegalie patiënten zijn sterk gecorreleerd aan de kwaliteit van leven parameters, zoals we eerder ook al zagen bij patiënten in remissie van het syndroom van Cushing (Hoofdstuk 2).
Acromegalie patiënten in remissie rapporteerden meer positieve ziektepercepties dan patiënten in remissie van het syndroom van Cushing. Het is verleidelijk om te speculeren dat er ziektespecifieke kenmerken bestaan bij ziektepercepties, naast meer algemene invloeden met betrekking tot klachten of chroniciteit. Verder is het ook verleidelijk te speculeren dat wellicht bij sommige andere endocriene ziekten dergelijke verstoringen in ziektepercepties bestaan.

Het is belangrijk dat endocrinologen aan patiënten uitleggen wat de oorzaak van acromegalie is. Ook zou de endocrinoloog feedback aan de patiënt moeten vragen naar diens overtuiging met betrekking tot de oorzaak van acromegalie. De ziektepercepties van patiënten, waaronder die met betrekking tot de vermeende oorzaak van acromegalie, zijn gebaseerd op verschillende bronnen. Dit betekent dat ziektepercepties niet noodzakelijkerwijs de feitelijke medische status of oorzaak van acromegalie weergeven.
De beschreven studie is belangrijk, omdat patiënten met acromegalie een verminderde kwaliteit van leven hebben, zelfs na langdurige remissie. De somatische en psychologische factoren die bijdragen tot een vermindering van de kwaliteit van leven zijn niet bekend, maar waarschijnlijk spelen klachten aan het bewegingsapparaat, hypofysaire insufficiëntie en ziektepercepties een rol.

We concluderen dat er een sterke correlatie bestaat tussen ziektepercepties en kwaliteit van leven bij patiënten in remissie van het syndroom van Cushing en bij patiënten in biochemische remissie van acromegalie. Patiënten in remissie van het syndroom van Cushing rapporteren meer negatieve ziektepercepties dan de verschillende referentie groepen met acute en chronische ziekten uit de literatuur. Patiënten in remissie van acromegalie rapporteerden meer negatieve ziektepercepties dan patiënten met een acute aandoening, maar meer positieve ziektepercepties dan patiënten met chronische aandoeningen, waaronder het syndroom van Cushing. We postuleren dat een gerichte zelfmanagement interventie zou kunnen helpen bij het verbeteren en bijsturen van negatieve ziektepercepties. Dit zou kunnen leiden tot een verbeterde kwaliteit van leven, althans ten dele, bij patiënten in remissie van het syndroom van Cushing of acromegalie.

3. Copingstrategieën

In Hoofdstuk 4 hebben we de copingstrategieën van patiënten na de behandeling van hypofysaire adenomen onderzocht. We hebben de Utrechtse Coping Lijst gebruikt om de verschillende copingstrategieën in kaart te brengen. De resultaten van deze studie laten zien dat patiënten na behandeling voor een hypofyse adenoom minder actieve copingstrategieën gebruiken, meer problemen proberen te vermijden en minder sociale steun zoeken in vergelijking met een aselecte steekproef uit de Nederlandse bevolking. In vergelijking met patiënten met chronische pijn zochten hypofyse patiënten meer sociale steun. Behandelde hypofyse patiënten werden ook vergeleken met patiënten die onder behandeling zijn bij een eerstelijns psycholoog en met patiënten met chronische pijn. Hypofyse patiënten scoorden lager op vermijden, het zoeken van sociale steun, passieve coping en het uiten van emoties, maar hoger op actieve coping. Dit betekent dat patiënten die werden behandeld voor een hypofyse adenoom, minder effectieve copingstrategieën gebruiken in vergelijking met de normale bevolking, maar blijkbaar gebruiken zij wel effectiever copingstrategieën dan patiënten met chronische pijn en patiënten onder behandeling bij een eerstelijns psycholoog. Een tweede analyse toonde aan dat patiënten na behandeling voor de ziekte van Cushing, acromegalie, en niet-functionerend hypofyse adenoom (NFA) bijna niet van elkaar verschilden met betrekking tot copingstrategieën. Het enige verschil was op het gebied van sociale steun: patiënten behandeld voor de ziekte van Cushing zochten meer sociale steun dan de patiënten behandeld voor NFA.
Dit is de eerste studie die zich richt op copingstrategieën bij patiënten behandeld voor een hypofyse adenoom. Wij zijn van mening dat informatie over de copingstrategieën van deze patiënten erg belangrijk is, omdat zij lijden aan chronische beperkingen ondanks genezing van hun initiële hypofyse adenoom. Deze beperkingen zijn vaak onbegrepen en moeilijk te behandelen. Kennis over het ge-

bruik van bepaalde copingstrategieën kan worden gebruikt bij het ontwerpen van een interventie op basis van bijvoorbeeld cognitieve gedragstherapie, zelfmanagement en de verstrekking van informatie over de negatieve effecten van de ziekte. We denken dat een dergelijke gerichte interventie kan leiden tot een betere kwaliteit van leven.

Concluderend kunnen we zeggen dat patiënten die behandeld zijn voor de ziekte van Cushing, acromegalie, of NFA andere en minder effectieve copingstrategieën gebruiken dan gezonde controles. Vergeleken met patiënten met chronische pijn en patiënten onder behandeling bij een eerstelijns psycholoog, rapporteren patiënten met een hypofyse adenoom iets beter copingstrategieën. Het zou belangrijk kunnen zijn om een training gericht op ziektepercepties, copingstrategieën en zelfmanagement vaardigheden te ontwikkelen, toe te passen en te evalueren voor hypofyse patiënten.

4. Cognitief functioneren

In Hoofdstuk 5 hebben we ons gericht op het cognitief functioneren van patiënten in remissie van de ziekte van Cushing. We hebben elf cognitieve testen gebruikt om het gehele spectrum van cognitie te onderzoeken. We hebben patiënten in remissie van de ziekte van Cushing met gematchte controles en met patiënten na de behandeling voor NFA vergeleken door middel van Z-scores. De resultaten toonden aan dat cognitief functioneren verminderd is bij patiënten na curatie van de ziekte van Cushing. Deze patiënten rapporteerden beperkingen in het dagelijks leven met betrekking tot geheugen, wat ook bevestigd werd door de cognitieve testen die we afnamen. Ook werden er beperkingen in bepaalde aspecten van het executief functioneren gevonden vergeleken met gematchte controles. Deze beperkingen zijn niet alleen gerelateerd aan hypofyse ziekte in het algemeen. Patiënten in remissie van de ziekte van Cushing bleken ook een verminderde cognitieve functie te vertonen in vergelijking met patiënten die behandeld zijn voor NFA. Deze waarnemingen geven aan dat er waarschijnlijk onomkeerbare effecten zijn die het gevolg zijn van eerder hypercortisolisme op het cognitief functioneren, en dus op het centrale zenuwstelsel.
Verschillende klinische kenmerken beïnvloedden de uitkomstparameters. Hypofyse uitval werd geassocieerd met verminderd executief functioneren. Verder waren hydrocortison afhankelijkheid en aanvullende radiotherapie negatief geassocieerd met het geheugen en executief functioneren, terwijl de duur van de remissie geheugen en executief functioneren positief beïnvloedde.

Langdurige blootstelling aan een overmaat van glucocorticoïden kan het functioneren van neurotransmitters en de neuronale structuur van het centrale ze-

nuwstelsel beïnvloeden. Bij knaagdieren werden schade aan de hippocampus en lange termijn potentiatie en een afname van hippocampale synaptische plasticiteit vastgesteld ten gevolge van chronische blootstelling aan hoge niveaus van glucocorticoïden. Bij de mens is een endogene actieve ziekte van Cushing geassocieerd met cognitieve stoornissen. De hippocampus is een van de meest gevoelige structuren voor glucocorticoïden in de hersenen en is cruciaal in het cognitief functioneren. De aanhoudende stoornissen in het cognitief functioneren bij patiënten met een behandelde ziekte van Cushing kunnen verklaard worden door de onomkeerbare effecten van het eerdere glucocorticoïd overschot op het centrale zenuwstelsel, met name de hippocampus. Verder onderzoek, waaronder functionele MRI en post-mortem analyses van het centrale zenuwstelsel zijn nodig om de gevolgen van eerdere glucocorticoïden blootstelling op belangrijke hersengebieden te evalueren.

In Hoofdstuk 8 hebben we een cross-sectionele studie beschreven waarin we cognitief functioneren onderzochten bij patiënten in langdurige biochemische remissie van acromegalie. We hebben deze patiënten vergeleken met gematchte controles en met patiënten na behandeling voor NFA door middel van Z-scores. We vonden geen verschillen in cognitief functioneren tussen patiënten in remissie van acromegalie en gematchte controles of NFA patiënten. Dit is in tegenstelling tot patiënten in remissie van de ziekte van Cushing, die wel last hebben van verminderd cognitief functioneren (Hoofdstuk 5). Gezien de design van de studie, is het waarschijnlijk dat deze verschillen in cognitieve functioneren tussen de patiënten na behandeling van acromegalie en patiënten na behandeling van de ziekte van Cushing worden verklaard door glucocorticoïd-specifieke onomkeerbare effecten op bepaalde hersenstructuren die betrokken zijn bij cognitieve functies, die blijkbaar niet beïnvloed worden door eerdere blootstelling aan GH/IGF-I overproductie.

Samenvattend zijn er subtiele stoornissen in het cognitief functioneren bij patiënten in remissie van de ziekte van Cushing in vergelijking met NFA patiënten en controles. De grootste problemen waren aanwezig in het geheugen, hoewel er ook problemen waren met het executief functioneren. Deze vermindering van de cognitieve functie na behandeling van de ziekte van Cushing is niet alleen het gevolg van een hypofyse aandoening in het algemeen en/of de behandeling daarvan, maar heeft ook te maken met specifieke elementen die waarschijnlijk worden veroorzaakt door de onomkeerbare effecten van het eerdere glucocorticoïd overschot op het centrale zenuwstelsel. Echter, er waren geen verschillen in cognitief functioneren toen patiënten in remissie van acromegalie werden vergeleken met gematchte controles en NFA patiënten. We postuleren dat het eerdere GH/IGF-I overschot geen onomkeerbare effecten heeft op delen van het centrale zenuwstelsel die belangrijk zijn voor het cognitief functioneren.

5. Prevalentie van psychopathologie

In Hoofdstuk 6 hebben we de prevalentie van psychopathologie en maladaptieve persoonlijkheidstrekken bij patiënten in remissie van de ziekte van Cushing bestudeerd. We hebben een aantal gevalideerde vragenlijsten gebruikt om psychopathologie te meten: de Apathie Schaal, de Prikkelbaarheid Schaal, de Hospital Anxiety and Depression Scale, en de Mood and Anxiety Symptom Questionnaire (verkorte vorm). We hebben de Dimensional Assessment of Personality Pathology (verkorte vorm) gebruikt om persoonlijkheidstrekken in kaart te brengen.
De studie liet zien dat patiënten in remissie van de ziekte van Cushing een hogere prevalentie van psychopathologie en maladaptieve persoonlijkheidstrekken hebben in vergelijking met gematchte controles. Daarnaast hebben patiënten in remissie van de ziekte van Cushing een hogere prevalentie van psychopathologie en maladaptieve persoonlijkheidstrekken dan patiënten die behandeld zijn voor NFA. Dit geeft aan dat de aanwezigheid van psychopathologie en maladaptieve persoonlijkheidstrekken niet alleen gerelateerd is aan hypofyse tumoren en/of de behandeling in het algemeen. Het is aannemelijk dat de lange termijn effecten van de ziekte van Cushing op psychopathologie en persoonlijkheidskenmerken het gevolg zijn van het eerdere glucocorticoïd overschot. Deze waarnemingen wijzen op de onomkeerbare effecten van eerder glucocorticoïd overschot op het centrale zenuwstelsel.

In Hoofdstuk 7 hebben we de huidige literatuur over psychopathologie en de ziekte van Cushing bekeken. Een actieve ziekte van Cushing gaat gepaard met een hoge prevalentie van psychopathologie, met name atypische depressie. Behandeling met glucocorticoïd verminderende/blokkerende middelen kan snel verlichting geven van de symptomen. Na een succesvolle operatie neemt de prevalentie van psychopathologie af, maar stemming en gedrag lijken niet te normaliseren. Na langdurige remissie rapporteren patiënten met de ziekte van Cushing nog steeds verminderde kwaliteit van leven en verminderde cognitieve functies.

In Hoofdstuk 8 beschrijven we de prevalentie van psychopathologie en maladaptieve persoonlijkheidstrekken, evenals cognitief functioneren (zie ook IV. Cognitief functioneren) van patiënten in remissie van acromegalie. We gebruikten dezelfde gevalideerde vragenlijsten als in de studie beschreven in Hoofdstuk 6: de Apathie Schaal, de Prikkelbaarheid Schaal, de Hospital Anxiety and Depression Scale, en de Mood and Anxiety Symptom Questionnaire (verkorte vorm). We hebben de Dimensional Assessment of Personality Pathology (verkorte vorm) gebruikt om persoonlijkheidskenmerken in kaart te brengen. De studie toonde aan dat patiënten na behandeling van acromegalie een hogere prevalentie van psychopathologie en maladaptieve persoonlijkheidstrekken lieten zien dan gematchte

controles. Patiënten na behandeling van acromegalie toonden ook meer psychopathologie, en vooral meer maladaptieve persoonlijkheidstrekken, in vergelijking met patiënten behandeld voor NFA. Deze waarnemingen geven aan dat de verhoogde prevalentie van psychopathologie en maladaptieve persoonlijkheidstrekken van patiënten na behandeling van acromegalie niet louter veroorzaakt wordt door een hypofyse adenoom per se en/of de behandeling daarvan, maar eerder door de overmatige blootstelling aan GH en/of IGF-I. We speculeren dat de resultaten van ons onderzoek de klinische indruk bevestigen dat patiënten in remissie van acromegalie andere en meer ernstige klachten hebben dan patiënten met NFA, hoewel de patiënten behandeld voor NFA een hogere incidentie hebben van hypofyse uitval.

Bovenstaande resultaten samengevat rapporteren patiënten in remissie van de ziekte van Cushing een hoge prevalentie van psychopathologie, in vergelijking met zowel de gematchte controles als patiënten die behandeld zijn voor NFA. Bovendien hebben patiënten in remissie van de ziekte van Cushing een hogere prevalentie van maladaptieve persoonlijkheidstrekken. Daarnaast rapporteren patiënten na behandeling van acromegalie ook een hoge prevalentie van psychopathologie, in vergelijking met gematchte controles. Patiënten na behandeling van acromegalie rapporteren een hogere prevalentie van maladaptieve persoonlijkheidstrekken, zowel in vergelijking met gematchte controles als patiënten behandeld voor NFA. De resultaten geven aan dat er onomkeerbare effecten zijn van eerder glucocorticoïd dan wel GH en/of IGF-I overschot op het centrale zenuwstelsel. Toekomstige studies zouden moeten onderzoeken of en hoe glucocorticoïden en GH/IGF-I veranderingen in (subklinische) psychopathologie teweeg kunnen brengen.

6. Slotopmerkingen

Dit proefschrift beschrijft de lange termijn effecten van hypofyse ziekten vanuit een psychologisch perspectief.

Uit de studies beschreven in dit proefschrift concluderen we dat:

- Patiënten in remissie van de ziekte van Cushing hebben meer negatieve ziektepercepties dan patiënten met acute en chronische aandoeningen.
- Patiënten in remissie van acromegalie hebben meer negatieve ziektepercepties dan patiënten met acute aandoeningen.
- Ziektepercepties en kwaliteit van leven zijn sterk gecorreleerd bij patiënten in remissie van de ziekte van Cushing, evenals bij patiënten in remissie van acromegalie.
- Patiënten die behandeld zijn voor een (niet) functionerend hypofyse ade-

noom, gebruiken andere en minder effectieve copingstrategieën dan gezonde controle personen.
- Patiënten in remissie van de ziekte van Cushing vertonen subtiele stoornissen in het cognitief functioneren in vergelijking met controle personen en patiënten met niet functionerende hypofyse adenomen.
- Patiënten in remissie van acromegalie verschillen niet in cognitief functioneren met controle personen en patiënten behandeld voor niet-functionerende hypofyse adenomen.
- Patiënten in remissie van de ziekte van Cushing of van acromegalie vertonen een hoge prevalentie van psychopathologie en maladaptieve persoonlijkheidstrekken in vergelijking met controle personen en patiënten met niet-functionerende hypofyse adenomen.

Tegenwoordig kunnen hypofyse adenomen goed worden behandeld, maar de patiënten houden een verminderde kwaliteit van leven ondanks langdurige remissie of genezing.
Bij patiënten in remissie van de ziekte van Cushing, het syndroom van Cushing of acromegalie moeten artsen zich bewust zijn van subtiele cognitieve stoornissen en een hoge prevalentie van psychopathologie en maladaptieve persoonlijkheidstrekken. Bovendien blijken deze patiënten ineffectieve copingstrategieën te gebruiken en hebben zij negatieve ziektepercepties die niet altijd correct zijn. Patiënten worden 'genezen' verklaard, maar ervaren nog steeds chronische beperkingen als gevolg van hun hypofyse aandoening. Artsen moeten overwegen deze patiënten veel beter te informeren over deze duidelijk miskende gevolgen op lange termijn. De artsen fungeren daarmee als gids in het 'acceptatie proces' van de patiënt. In ieder geval wordt de patiënt aldus optimaal van informatie voorzien, hetgeen behulpzaam kan zijn bij de acceptatie van de ziekte en de kennelijke gevolgen daarvan. Het is mogelijk dat een andere aanpak daarnaast ook effectief zou kunnen zijn. Een multidisciplinaire aanpak met endocrinologen, psychologen en maatschappelijk werkers zou wellicht ook de acceptatie en het omgaan met de gevolgen van een hypofyse aandoening kunnen bevorderen.
Wij denken dat de ontwikkeling van een zelfmanagement interventie, waaronder training van copingvaardigheden, voor patiënten met hypofyse ziekten goed zou werken. Deze interventie kan hypofyse patiënten helpen om te gaan met hun beperkingen en kan veranderingen teweeg brengen in ziektepercepties. Hoewel dit de onomkeerbare gevolgen van de hormoon producerende hypofyse ziekten niet zal kunnen wegnemen, postuleren we dat deze aanpak uiteindelijk kan leiden tot een betere kwaliteit van leven.

Curriculum Vitae

Jitske Tiemensma werd geboren op 3 januari 1985 te 's-Gravenhage. Zij groeide op in Zoetermeer, waar zij in 2003 haar VWO diploma haalde aan het Erasmus College. Datzelfde jaar startte zij met de opleiding psychologie aan de Universiteit Leiden. Na het schrijven van haar bachelorscriptie over de invloed van fysieke en subjectieve stress reacties op aandacht en werkgeheugen, behaalde zij in 2006 haar Bachelor of Science. Omdat Jitske erg geïnteresseerd was in het zenuwstelsel, besloot zij om de Research Master Neurosciences te volgen aan de Vrije Universiteit te Amsterdam. De titel Master of Science kwam in 2008 in haar bezit na het schrijven van haar masterscriptie getiteld 'Neuropsychological, psychiatric, and personality changes in acromegaly: a review'.
Vanaf september 2008 was Jitske als onderzoeker in opleiding verbonden aan de afdeling Endocrinologie en Metabolisme van het LUMC, onder leiding van Prof. dr. J.A. Romijn, Dr. A.M. Pereira en Dr. N.R. Biermasz. Tijdens het promotie traject werden haar een Young Investigator Award, een prijs voor het beste artikel in de klinische endocrinologie, een plek in de Endocrine Trainee Day – Class of 2010 voor veelbelovende PhD-studenten te San Diego en vele reisbeurzen toegekend. Ook werd zij genomineerd voor diverse poster prijzen tijdens internationale congressen.
Vanaf april 2012 gaat Jitske onderzoek doen bij University of California in Merced.

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