

Cognitive impairment and psychopathology in patients with pituitary diseases

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ABSTRACT

Patients who are considered to have been successfully treated for pituitary disease because they are in long-term remission of functioning or non-functioning macroadenomas, still report reduced quality of life and persistent morbidity and have (slightly) increased mortality. It is likely that the causes are multi-factorial, including intrinsic imperfections of surgical or endocrine replacement therapy, but also of persistent effects of hormone excess on the central nervous system affecting personality and behaviour. In agreement, recent studies demonstrate that patients in long-term remission for acromegaly and Cushing's disease have a higher prevalence of psychopathology and more maladaptive personality traits, display different and less effective coping strategies, and experience more negative illness perceptions. These new findings are intriguing in view of the general impairments in health-related quality of life, suggesting that the effects of previous hormone excess on the central nervous system can be long-lasting and to a certain extent even be irreversible. This review aims to address the effects of the treatment of pituitary disease on quality of life and neuropsychological functioning. Further research is needed to gain more insight into irreversibility of hormone excess syndromes. However, since coping strategies are altered, it is tempting to speculate that quality of life might be improved by targeted interventions.

KEYWORDS

Cognition, psychopathology, Cushing, acromegaly, pituitary adenoma

INTRODUCTION

Pituitary adenomas are neuroendocrine tumours. Neuroendocrine tumours represent a heterogeneous group of tumours that also include carcinoid tumours, non-carcinoid

tumours of the gastrointestinal tract (such as insulinomas and gastrinomas), tumours of the autonomic nervous system (paragangliomas, pheochromocytomas), and medullary thyroid carcinoma.¹ Neuroendocrine tumours usually retain the characteristics of the original endocrine tissue, and thus often produce hormones and express hormone receptors. In addition, they grow slowly and often exhibit a specific genetic pattern. Functioning pituitary tumours cause the clinical syndromes of acromegaly (growth hormone (GH)), Cushing's disease (ACTH), prolactinoma (prolactin) and secondary hyperthyroidism (thyroid-stimulating hormone) due to pathological secretion of the specific hormone. Approximately 50% of pituitary tumours are not endocrine active: the so-called non-functioning macroadenomas (NFMA). Although pituitary adenomas are benign tumours, they can cause serious morbidity due to overproduction of pituitary hormones and/or due to local mass effects resulting in pituitary insufficiency and optic chiasm compression. The treatment of pituitary adenomas includes transsphenoidal surgery, medical therapy (e.g. with somatostatin analogues, GH receptor antagonists or dopamine agonists), and/or radiotherapy.^{2,3} However, despite curative treatment of these adenomas *per se*, multiple physical and psychological symptoms may persist even when long-term remission has been present for many years. In this review, we will address the short- and long-term psychological consequences of pituitary adenomas in the Leiden cohort of patients who were in long-term remission after surgical cure but appeared to have persistent impairments in quality of life.

TREATMENT OF PITUITARY ADENOMAS: THE HISTORICAL PERSPECTIVE

Pituitary adenomas, especially Cushing's disease, result in severe comorbidity and highly increased mortality when left untreated.⁴ Although surgical tumour removal

was introduced by Harvey Cushing in the beginning of the 20th century, morbidity and mortality remained very high in this period. However, with the introduction of the microscopic transsphenoidal technique in the 1970s, surgical morbidity and mortality reduced dramatically (to below 1%). Nowadays, surgical treatment is the cornerstone of treatment for patients with pituitary adenomas.² Remission rates induced by transsphenoidal pituitary surgery in referral centres amounted to 50 to 70% for macroadenomas and 80 to 90% for microadenomas.⁵ The most important side effect of surgical treatment is new pituitary insufficiency, developing in 10 to 15% of patients. However, many patients with NFA, up to 90%, and 10 to 50% of patients with functioning adenomas already have deficits preoperatively, some of which can be resolved after onset of cure (i.e. hypogonadism).⁶⁻⁸

When surgery does not lead to remission, radiotherapy or medical treatment, such as somatostatin analogues, dopamine agonists or pegvisomant, are available for functioning tumours. Depending on the disease, medical treatment has a more or less prominent role. For prolactinoma, dopamine agonists are the treatment of choice. For acromegaly, somatostatin analogues are either first or second choice, followed by pegvisomant if needed, reserving radiotherapy for selected cases. For Cushing's disease, either reoperation or irradiation are secondary treatment options. New developments suggest Pasireotide as potential treatment for Cushing's disease.

Hormone insufficiency is diagnosed by dynamic testing and hormone deficits are replaced if necessary using hormone replacement therapy, including GH, usually resulting in dramatic improvement in quality of life and symptoms. However, quality of life fails to normalise in the long term, and we do not yet exactly know why this is the case. Intrinsic imperfections of endocrine replacement therapy is one possibility but potential long-lasting effects of hormones on the central nervous system affecting personality and behaviour has not been considered until recently, although psychological disturbances had already been reported in patients with pituitary adenomas 100 years ago.⁹ However, now that the final outcome is expected to be nearly normal health, the focus on an unsatisfactory degree of remission has regained much attention.¹⁰

MORTALITY IN OPTIMALLY TREATED PATIENTS

In the Leiden cohort of patients treated for pituitary adenomas, we addressed the long-term consequences of these diseases and their treatment. Based on these clinical observations, the question arose whether remission in the long term equals cure. If that were the case, mortality would have to be normal and as well as disease-related morbidity, in this case with a focus on the long-term

mental sequelae. A Kaplan-Meier Survival Curve can best illustrate mortality. In the Leiden series of patients who were treated by a single neurosurgical procedure by the same neurosurgeon for either acromegaly, Cushing's disease or NFA, we documented the number of observed deaths and compared these with the expected number of deaths obtained from the Dutch population.¹¹ This obtained standardised mortality ratio was 1.24 for NFA, indicating a 24% increased death rate. For acromegaly, the standard mortality ratio was 1.32, whereas for Cushing's disease the increase in mortality was even significantly higher: 80%. These observations point towards long-lasting hormone-specific effects, especially of cortisol overexposure, on mortality, despite long-term remission.

PITUITARY HORMONES, THE STRESS RESPONSE AND BEHAVIOUR

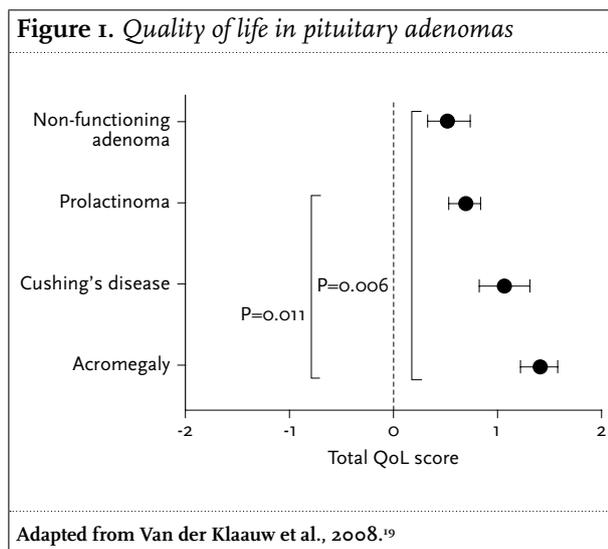
When focusing on mental sequelae in endocrine disease, it is crucial to realise that from an evolutionary point of view, a normal stress response is a prerequisite for normal adaptive behaviour.¹² The main mediator of the stress response is cortisol (or corticosterone in rodents). When an individual is exposed to a stressor, changes occur rapidly within seconds to minutes through stimulation of the sympathetic nervous system and cortisol secretion. In addition, the stress response is characterised by slower changes (that occur within minutes to hours) via stimulation of both the mineralocorticoid and glucocorticoid receptors in the central nervous system. In the end, all these changes occur only with the purpose to induce the required behavioural adaptations in order to enable the individual to adequately cope with the stressor. However, when a stressor becomes chronic, a so-called vulnerable phenotype develops that is characterised by neurodegenerative changes and cognitive impairment.¹²

It is not surprising that Cushing's disease, which can be considered *the* clinical human monosymptomatic equivalent for severe chronic stress, is associated with behavioural abnormalities. In addition, patients with NFA can be considered to be a model for the consequences of pituitary insufficiency *per se*, because of the high rate of hypopituitarism present in these patients. In this respect it is intriguing that one of the most potent physiological stressors is hypoglycaemia. During an insulin tolerance test (ITT), the induction of hypoglycaemia is able to evoke all classical features of the stress response characterised by catecholamines and cortisol secretion. The insulin-induced hypoglycaemia test, however, is also a very potent stimulator of GH secretion, and is therefore considered to be the golden standard test for the diagnosis of cortisol and GH deficiency.^{13,14} Thus, by definition, patients with cortisol and GH excess or deficiency cannot exhibit a

normal stress response, and are likely to represent human models for the effects of impaired stress responsiveness on psychopathology and cognitive function.

QUALITY OF LIFE AND PSYCHOLOGICAL FUNCTIONING

In the last decade, quality of life (QoL) was evaluated in the Leiden cohort of patients with pituitary adenomas using general health-related questionnaires both in untreated and treated disease. These studies demonstrated that QoL generally improves after treatment, but also that QoL remains impaired even after successful treatment, with disease-specific features (*figure 1*).¹⁵⁻¹⁸ It appeared that patients treated for acromegaly were most impaired in QoL, when compared with patients treated for Cushing's disease, prolactinoma or patients treated for NFA.¹⁹ However, these results were obtained using general health questionnaires and not disease-specific ones. Specifically, patients treated for acromegaly predominantly reported impairment in physical performance and an increase in bodily pain, whereas patients treated for Cushing's disease also reported impairments in physical functioning. In addition, these QoL studies revealed psychological impairments on various quality of life questionnaires, both in general health and disease-specific questionnaires. As stated previously, the QoL questionnaires are not designed for an in-depth assessment of psychological functioning. Whereas the biological effects of cortisol and GH excess on psychological functioning have been reported in several studies in untreated Cushing's disease and acromegaly and in some studies after short-term remission,²⁰ it was unknown if, and to which extent, cognitive dysfunction and psychopathology was present in these patients in the long term.



PSYCHOLOGICAL FUNCTIONING IN CUSHING'S DISEASE

In agreement with the crucial role of cortisol in the regulation of the stress response, patients with active Cushing's disease do manifest cognitive impairments, especially in the memory domain. In addition, psychopathology and maladaptive personality traits are often observed during the active phase of Cushing's disease. Previous studies reported impairments in memory, visual and spatial information, reasoning, verbal learning, and language performance.²¹⁻²⁴ Structures important in cognitive functioning, such as the hippocampus and cerebral cortex, are rich in glucocorticoid receptors and are therefore particularly vulnerable to the cortisol excess present in Cushing's disease.^{12,23,25} 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 behavioural and cognitive functions, due to functional and, over time, structural alterations in specific brain target areas.^{26,27} A limited numbers of studies that have reported the effects of treatment indicate that significant improvements in both physical and psychiatric symptoms occur within the first year after successful surgery.²⁰

PSYCHOLOGICAL FUNCTIONING IN ACROMEGALY

GH and IGF-1 receptors are widely distributed throughout the central nervous system, including the limbic system and the frontal lobe.^{28,29} In accordance, impaired cognitive function and maladaptive personality have also been documented in patients with active acromegaly.³⁰⁻³² In addition, substitution of GH-deficient patients with recombinant human GH resulted in a rapid and sustained amelioration of cognitive functioning and general well being.^{33,34} However, in active acromegaly, many of the systemic changes induced by GH and/or IGF-1 excess, such as arthropathy and cardiac valvulopathy, are not completely reversed upon successful treatment of acromegaly,^{35,36} 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 that were considered cured from acromegaly showed elevated scores for anxiety and depression.¹⁵

ADDITIONAL OBSERVATIONS AND MISCLASSIFICATIONS OF PSYCHOPATHOLOGY IN PITUITARY PATIENTS

Pituitary disease and/or its treatment can affect mood and personality changes by disrupting the connections

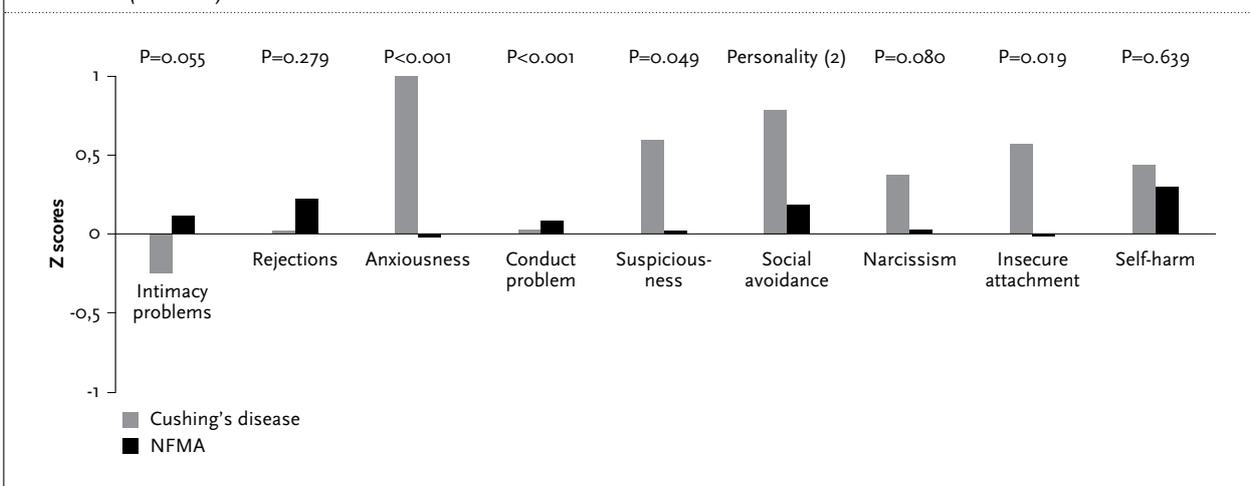
between the prefrontal cortex with other limbic structures, thereby impairing the behavioural control exerted by the prefrontal cortex on the limbic system.³⁷ The literature reports on such anecdotal cases, for instance by Weitzner *et al.*³⁸ who reported on patients with pituitary disease and apathy syndrome, patients who had previously been incorrectly classified as having major depressive disorder and had been treated accordingly with antidepressants for a long period of time. This, together with our general impression that patients treated for Cushing's disease behave differently when compared with patients treated for other pituitary adenomas, we hypothesised that hormone-specific effects may be long-lasting or even be irreversible.

COGNITIVE FUNCTION AND PSYCHOPATHOLOGY DURING LONG-TERM FOLLOW-UP

Specifically, we hypothesised that patients with a long-term cure of both Cushing's disease and acromegaly showed cognitive dysfunction, persistent psychopathology and maladaptive personality traits. For this purpose, we studied patients cured of Cushing's disease and of acromegaly and age- and gender-matched controls. In addition, we included patients treated for non-functioning pituitary macroadenomas (NFMA) and additional controls, matched to these patients for age and gender. The cognitive evaluation consisted of multiple tests, which evaluated global cognitive functioning, memory, and executive functioning. In patients treated for Cushing's disease, cognitive function, reflecting memory and executive functions, was impaired despite long-term remission.³⁹

These findings were not replicated in patients successfully treated for acromegaly.⁴⁰ We then decided to extend these observations and asked patients and controls to complete questionnaires focusing on frequently occurring psychiatric symptoms in somatic illness including the Apathy Scale, Irritability Scale, Hospital Anxiety and Depression Scale (HADS), and Mood and Anxiety Symptoms Questionnaire short-form (MASQ-30). Personality was assessed using the Dimensional Assessment of Personality Pathology short-form (DAPP). After a mean remission duration of 13 years for both Cushing's disease and acromegaly, patients cured from Cushing's disease (compared with matched controls) scored significantly worse on virtually all questionnaires. Compared with NFMA patients, patients treated for Cushing's disease scored worse on apathy, irritability, negative affect and lack of positive effect, somatic arousal, and 11 out of 18 subscales of the personality scales.⁴¹ Patients cured of acromegaly (compared with matched controls) scored significantly worse on virtually all psychopathology questionnaires and on several subscales of the personality scales. These differences, although less accentuated, were also found when the patients cured of acromegaly were compared with NFMA patients.⁴⁰ In patients with prolactinomas, the impaired quality of life despite long-term biochemical control with dopamine agonists (and no surgical intervention!) is intriguing, because the current challenges in these patients relate to intrinsic imperfections of long-term medical treatment, and the fact that the disease recurs in the majority of the patients after withdrawal of dopamine agonist treatment.⁴² In agreement, others have now replicated our findings of altered personality profile, also in patients with prolactinomas.⁴³

Figure 2. Personality traits in patients treated for Cushing's disease and patients treated for non-functioning pituitary adenomas (NFMA)



The zero Z score represents the scores for the healthy matched control subjects. Adapted from Tiemensma *et al.*⁴²

COPING AND ILLNESS PERCEPTIONS

Previous studies in other (chronic) diseases have indicated that QoL and psychological factors, such as illness perceptions and psychopathology, are related. Coping strategies may affect quality of life that is impaired in patients treated for pituitary adenomas. Additionally, illness perceptions pertain to the pattern of beliefs patients develop about their illness. Illness perceptions are also determinants of quality of life (QoL), but factors contributing to persisting impaired QoL after treatment for pituitary disease remain largely unknown. Therefore, coping strategies and illness perceptions, as potentially modifiable psychological factors, were explored in relation to QoL in patients after long-term remission of pituitary disease. In the first study,⁴⁴ patients treated for Cushing's disease, for acromegaly and for NFMA, were compared with three reference populations: an a-select sample from the Dutch population, patients with chronic pain, and patients receiving primary care psychology services. Furthermore, the three patient groups were compared with each other. The Utrecht Coping List assessed coping strategies. Patients with pituitary adenomas (when compared with the a-select sample) reported less active coping, sought less social support, and reported more avoidant coping. 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. Thus, patients treated for pituitary adenomas

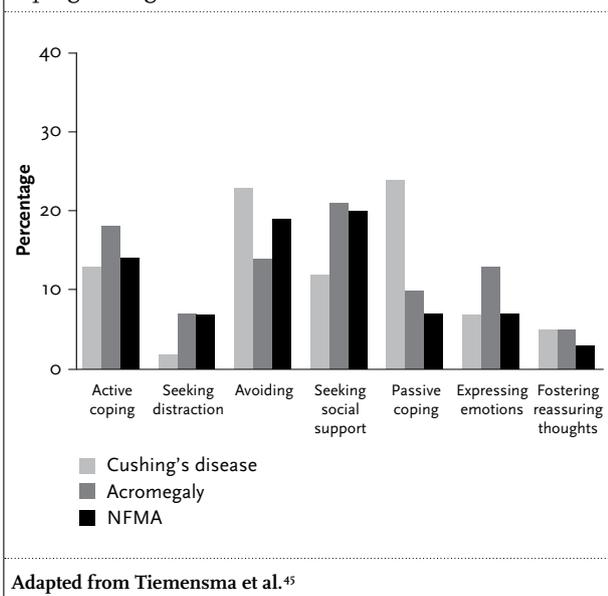
display different and less effective coping strategies compared with healthy controls.⁴⁴

Illness perceptions were evaluated using the Illness Perception Questionnaire (IPQ)-Revised, and QoL was measured using the physical symptom checklist, EuroQoL-5D (EQ-5D), and the CushingQoL. Reference data were derived from recent studies and included patients with vestibular schwannoma, acute or chronic pain, and chronic obstructive pulmonary disease (COPD). Illness perceptions strongly correlated with QoL. Patients with either acromegaly or CS had negative illness perceptions compared with patients with vestibular schwannoma and patients with acute pain, and also reported more illness-related complaints.^{45,46} 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. Noteworthy, patients after remission of acromegaly had a good understanding of their disease, but they experienced a lack of personal control and were not likely to seek medical care.⁴⁶

CONCLUSION

Patients who are considered to be successfully treated for pituitary disease show a higher prevalence of psychopathology and more maladaptive personality traits, suggesting that the effects of previous glucocorticoid and GH excess on the central nervous system can be long lasting and even irreversible. The additional observations that patients treated for pituitary adenomas also display different and less effective coping strategies and experience more negative illness perceptions are intriguing in view of the general impairments in health-related quality of life. It is tempting to speculate that quality of life might be improved by targeted interventions that could help to stimulate patients to use a more active coping strategy and to seek social support instead of an avoiding coping strategy, and by addressing illness perceptions, for example, by a self-management intervention program.

Figure 3. Different personality traits result in different coping strategies



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