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## **Pituitary diseases : long-term psychological consequences**

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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, Gieffens 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 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.

Flisch, 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 Persönlichkeitsinventar, State-trait-anxiety-inventory, Rosenzweig picture frustration test, Befindlichkeitskala, 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.
Somino, 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 Scheingart (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 CAT-EGO 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)

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

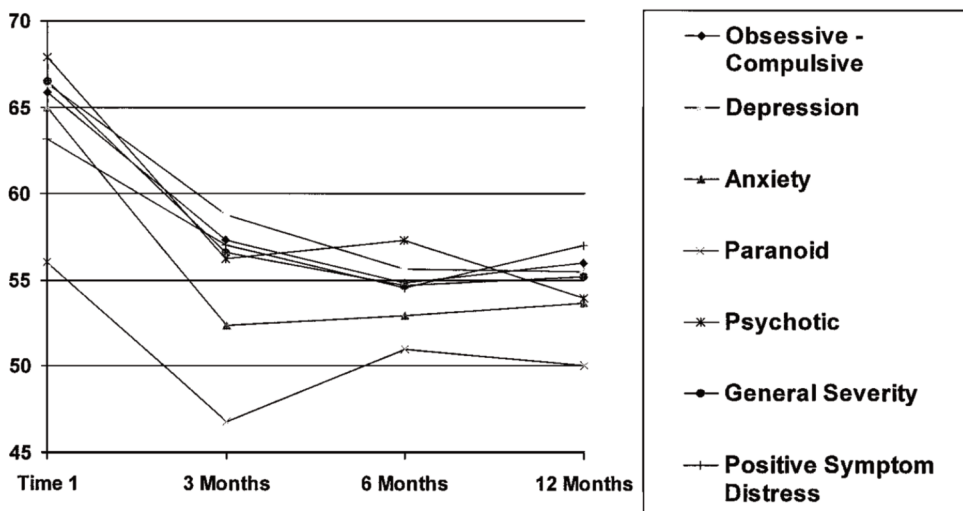
NS, not significant; 1, by  $\chi^2$  or t test; 2, data available in 115 cases

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 effectiveness 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 relieve 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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