Chapter 5

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

Jitske Tiemensma, Nieke E. Kokshoorn,
Nienke R. Biermasz, Bart-Jan S.A. Keijser,
Moniek J.E. Wassenaar, Huub A.M. Middelkoop,
Alberto M. Pereira, Johannes A. Romijn

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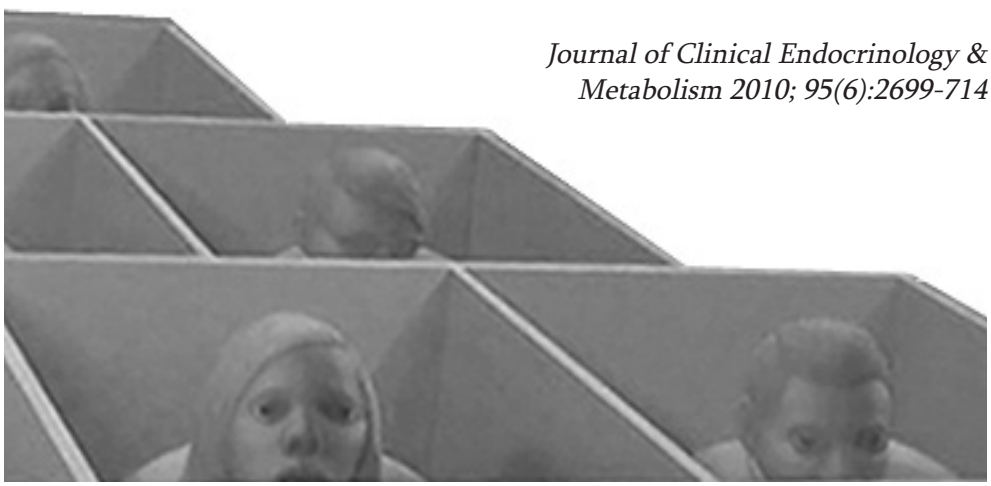

Abstract

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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